EXHIBIT 16

BRIEFING DOCUMENT FOR THIAZOLIDINEDIONE/ROSIGLITAZONE PUBLIC ADVISORY COMMITTEE MEETING

From: Karen M. Mahoney, M.D.
Mary H. Parks, M.D.
Division of Metabolism and Endocrinology Products

Through: Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II

To: Endocrine Metabolic Drugs Advisory Committee members
Drug Safety and Risk Management Advisory Committee
Invited Panelists

Date: July 9, 2007

INTRODUCTION

In August 2006, GlaxoSmithKline (GSK) submitted to the FDA a completed meta-analysis of 42 controlled clinical trials involving rosiglitazone (RSG) use in patients with type 2 diabetes mellitus (T2DM). This analysis was undertaken by GSK as a result of a 2003 World Health Organization report of a data mining signal for increased cardiac risk, including heart failure, for the thiazolidinedione (TZD) drug class. The overall findings from the meta-analysis, as conducted by GSK, suggested an increased risk for myocardial ischemia. Submitted in the same application as the meta-analysis was an observational cohort study, which did not confirm a signal of eoncern associated with rosiglitazone for the risk of MI or coronary revascularization relative to other anti-diabetic therapies. This applieation has undergone extensive review by the agency with an internal Center-level briefing in April 2007 resulting in a recommendation for a public advisory committee meeting that was initially planned for the Fall 2007 that would cover cardiovascular risks in general with the TZD class (both ischemic risk and risk for heart failure). On May 18, 2007, the *New England Journal of Medicine* (NEJM) published on-line a separate meta-analysis of rosiglitazone trials performed by Nissen and Wolski on study level data with a reported 43% increased risk of myocardial infaretion (MI) and a 64% increased risk of cardiovascular (CV) death. This publication resulted in extensive press coverage and Congressional inquiries, including several interviews with multiple FDA scientists by Congressional staff during the on-going review process. As a result of the public considerable and understandable concern, the FDA is presenting data from completed and ongoing reviews to this Joint Advisory Committee comprised of members from Endocrine and Metabolie Advisory Committee, Drug Safety and Risk Management Committee, and specialists in cardiovascular disease from the CardioRenal Drugs Advisory Committee to gain expert advice on the cardiac ischemic risk of rosiglitazone. As this meeting is being convened several months earlier than planned, time constraints preclude a thorough discussion of the risk of heart failure associated with rosiglitazone and pioglitazone. This memo and the presentations will focus only on cardiac isehemic risk, primarily foeused on rosiglitazone.

Ms. Joy Mele's FDA statistical review of the meta-analysis and her presentation will precede this memo and its clinical presentation. She has identified certain baseline patient characteristics, coneomitant medication use, and comparator groups that may contribute notably to the overall risk estimate in the

meta-analysis. The purpose of this memo is to present clinical data from large, prospective, controlled clinical trials that may aid in the interpretation of a finding of excess cardiac risk from the meta-analysis of 42 controlled studies.

Thiazolidinediones/PPAR-gamma agonists

Thiazolidinediones (TZDs) are selective ligands of the nuclear transcription factor peroxisome-proliferator-activator-receptor-γ (PPAR-γ). Also referred to as PPAR- γ agonists, these drugs have been developed to target the insulin resistance associated with type 2 diabetes mellitus (T2DM); however, TZDs have also been studied in other insulin-resistant states including polycystic ovarian syndrome and more recently, the treatment of pre-diabetic states. To date, the FDA has reviewed four New Drug Applications (NDAs) for different compounds with PPAR-γ activity for the treatment of adults with T2DM. Troglitazone (Rezulin®) was approved in 1997 and initially showed promise with significant reductions in hemoglobin A1c (HbA1c) and improvements in insulin sensitivity, thus allowing many patients to avoid initiation of insulin or markedly reduce their daily dosing requirements. However, shortly after its approval, severe cases of hepatotoxicity were observed and in March 2000 the drug was withdrawn from the market due to an increased risk of liver failure resulting in death or necessitating liver transplantation. In 1999, the FDA approved rosiglitazone (Avandia®) and pioglitazone (Actos®). Clinical trial experience and elose post-marketing surveillance of these two compounds have shown an absence of the unacceptable risk of hepatotoxicity seen with troglitazone. On average, the expected HbA1c reductions with these agents range from 0.5 to 1.5% with effect sizes variable by patient characteristics (e.g., drug-naïve vs. prior treatment, or monotherapy vs add-on therapy).

The fourth NDA was for the non-TZD, PPAR-α/γ agonist, muraglitazar (Pargluva®), where PPAR-α agonism was intended to impart favorable clinical effects on lipid parameters. This application was discussed at a public advisory committee in September 2005 where FDA expressed concerns over an imbalance in cardiovascular events and deaths in the phase 3 trials. Despite an overall recommendation for approval by the Endoerine and Metabolic Drugs Advisory Committee, an approvable action was issued. In May 2006, Bristol-Myers Squib announced the diseontinuation of this clinical development program.

Numerous Investigational New Drug Applications (INDs) have been submitted to the agency for drugs targeting PPAR-α or –γ receptors to treat T2DM and dyslipidemia. More recently, applications for pan-agonists targeting α, γ, and δ receptors have been submitted to treat the so-called metabolic syndrome, including obesity. As a class, PPAR agonists with gamma activity are associated with anemia, hemodilution, weight gain, edema, and exacerbation or development of heart failure. In addition, nonclinical studies have raised concerns regarding carcinogenic potential with evidence of multiple tumors (aeross multiple species and in both genders) observed with several of these compounds. Consequently, partial clinical holds are imposed on all these drugs requiring that two-year animal carcinogenicity studies be conducted and data submitted for review prior to initiation of clinical studies beyond 6 months' duration. Findings from many nonclinical studies have resulted in discontinuation of several INDs or have led to limitations in the maximal clinical dose for Phase 3 clinical trials. Reasons for cessation of clinical development for drugs in the PPAR class include findings in animals of tumors of the bladder, liver, and adipose tissue; muscle/skeletal toxieity (specifie to PPAR-α activity); cardiac myopathy and necrosis, and severe edema at doses consistent with the exposure range for human clinical doses. Aside from muraglitazar, a few programs have also been discontinued after renal and cardiac safety findings appeared with more extensive clinical trial experience in Phase 3 (tesaglitazar and farglitazar).

Similarly, the marketed TZDs, rosiglitazone and pioglitazone, are associated with anemia, weight gain, edema, and risk of heart failure. Unique to pioglitazone, which appears to have some α-agonistic activity, was an association with urinary bladder tumors in its carcinogenicity studies dosed at approximately 14x

the maximum recommended clinical dose. Benign and/or malignant transitional cell neoplasms were observed in male rats at doses equivalent to maximum recommended clinical dose based on mg/m^2. Two large placebo-controlled clinical studies have also observed an imbalance in the number of bladder cancers [6 pioglitazone (0.16%), 2 placebo (0.05%)], although there are not definitive data to date to conclude that the animal findings signal a significant clinical risk. These findings are in the labeling for pioglitazone, and the potential human correlates for the animal findings are continuing to be actively addressed.

Rosiglitazone

Rosiglitazone maleate was approved in 1999 for the treatment of T2DM in adults. Initial approval was for monotherapy use and as add-on to metformin in the setting of inadequate glycemic control with the single agent. Although rosiglitazone was not a first-in-class oral anti-diabetic, the NDA was under review during the safety deliberations over Rezulin® (troglitazone), and was therefore discussed before a public advisory committee. During the advisory committee meeting, discussions on safety focused on known concerns at that time: liver toxicity, anemia/hemodilution, fluid-retention/edema, and elevations in cholesterol (C) levels. Any concerns of cardiac ischemic safety at that time were based on the increases in total-C and low density lipoprotein cholesterol (LDL-C) observed with rosiglitazone, for which most members advised inclusion in labeling, with recommendations for monitoring of patients. No increased risk for direct cardiac ischemia was identified. There were non-clinical findings of cardiac toxicity consisting of increased heart weight, pericardial effusion, atrial thrombi, and CV deaths that were interpreted as due to heart failure observed across several different species. These signals were not evident in the pre-marketing clinical database which consisted of a total of 4598 patients exposed to rosiglitazone; 2061 of these patients received drug for at least 12 months. FDA and GSK agreed on a Phase 4 study commitment to further explore durability of efficacy and several safety issues, including hepatotoxicity and edema/heart failure. GSK diligently conducted this study, called ADOPT, and fulfilled the regulatory requirement regarding the postmarketing commitment. ADOPT is discussed subsequently in this memo.

The clinical development program for rosiglitazone has been extensive with numerous studies conducted in patients with T2DM since approval. Several of these studies were included in the meta-analysis submitted by GSK and have been previously reviewed by FDA. While the meta-analysis combines the findings from 42 controlled clinical studies with exposures in 14,237 patients (8604 on RSG/RSG-containing treatment vs 5633 on non-RSG containing treatment), the majority of the studies included in the meta-analysis were of short duration (average duration of exposure $\leq$ 180 days). Thirty studies were 6 months in duration, 8 were less than 6 months, and 4 were at least one year in duration (there was a single 2-year study). None of the studies in the meta-analysis was specifically designed to evaluate cardiovascular benefit and all but one had no prospective blinded committee adjudication of CV events. For the combined data from these 42 studies, a retrospective adjudication for cardiovascular adverse events (heart failure or myocardial ischemia) was undertaken in a blinded review of narratives for serious adverse events (SAEs) by physicians in a GSK Working Group and a cardiologist in an External Review Group. Blinded review of individual investigator-provided verbatim terms was also performed by GSK physicians. As stated in Ms. Mele's review, a recent different analysis of these 42 controlled trials was submitted to the Agency on May 31, 2007. In this analysis, GSK applied the composite endpoints of stroke, MI, and CV death to further assess risk between rosiglitazone and the comparators in this pooled database. Although this analysis has its limitations, particularly for identifying the stroke component, it is a commonly used composite in clinical trials evaluating cardiovascular risks and benefits of interventions, including the long-term, controlled studies discussed in this memo. This composite (referred to as MACE or APTC by different reviewers) allows for a similar endpoint for comparisons to be made across clinical trials and databases.

Not included in the meta-analysis are four large, prospective, long-term, controlled studies that were either completed *after* the cut-off date for inclusion in the meta-analysis or are still ongoing. Unlike the 42 studies in the meta-analysis, these studies had a prospective collection of CV events. Most of these studies had an endpoint adjudication committee prospectively reviewing CV events in a blinded fashion. These four studies, combined, will yield data for approximately 16,000+ patients studied for approximately 3 to 5 years. These studies' combined patient-year exposure is several multiples that of the studies included in the meta-analysis. This briefing memo will describe these long-term, controlled clinical trials with respect to the following:

- status (completed vs ongoing; if completed, data available to FDA)
- study design
- study objective
- patient population
- study outcome, if available

In addition, this briefing memo will describe CV risk evaluation of the other marketed TZD, pioglitazone. Although there are no direct head-to-head CV outcomes studies comparing rosiglitazone to pioglitazone, these studies are important in the consideration of rosiglitazone's risk-benefit profile relative to other available therapies.

LONG-TERM CONTROLLED CLINICAL TRIALS WITH ROSIGLITAZONE

The following table summarizes the key features of the large controlled trials presented in this memo. Four of these employ rosiglitazone as the specific or predominant investigational TZD (ADOPT, DREAM, RECORD, and BARI-2D) and one study involves the use of pioglitazone (PROactive).

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones

	PROactive[1]	ADOPT[2]	DREAM[3]	RECORD[4]	BARI 2D[5]
Status of Trial	Complete, submitted to FDA, reviewed	Complete, submitted to FDA, review ongoing	Complete, not yet submitted to FDA	Ongoing	Ongoing
TZD Used	Pioglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone
Sponsor of Trial	Takeda	GSK	McMaster University, Canada	GSK	NHLBI
Status of Data	Full study report received by FDA, reviewed, labeled	Full study report received by FDA, review ongoing	Published, study report not yet received by FDA	Ongoing, interim safety analysis published	Ongoing
Primary Objective	"To demonstrate that pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus"	Evaluate and compare effects of long-term monotherapy of T2DM with RSG, SU and MET on improvement and mnt of glycemic control in patients with recently diagnosed T2DM	To assess prospectively whether rosiglitazone ean reduce the frequency of diabetes in individuals with impaired glucose tolerance, impaired fasting glucose, or both. Factorial design also examined ramipril effect.	Compare time to reach combined CV endpoint of CV death and/or CV hospitalization, between RSG-treated patients and non-RSG-treated patients, in patients with T2DM who are inadequately controlled on either MET or SU alone. First hypothesis noninferiority; then test for superiority.	Compare 5-year mortality for initial elective revascularization with aggressive medical therapy vs aggressive medical therapy alone; and to compare 5-year mortality for management of hyperglyeenua with strategy of insulin-sensitizing vs insulin-providing.
Secondary Objective(s) of Particular Relevance	Characterize safety in this grp of T2DM patients	Assess long-term safety (cardiovascular, liver, hematologic, weight, lipids)	Assess effect on CV and renal outeomes	Separate comparisons for RSG vs MET and RSG vs SU for coinposite of CV death and/or CV hospitalization.	Examine effect of revasc + med rx vs intensive med rx alone, and examine effect of insulin-sensitizing vs insulin-providing med rx, on nther CV endpoints (see below)
Number of Patients Randomized	5238	4351	5269	4447 (last randomized Apr 2003)	2368 (last randomized Mar 2005)
Duration	Mean 34.5 months	4 years originally planned; changed to 6 years due to higher-than-expected withdrawal rate and lower-than-expected monotherapy failure rate	Median 3 years	Planned median 6 years	Planned 5 years
Number of Centers (and Location[s])	321 (Europe)	473 (North America and Europe)	191 (North and South America, Europe, India, Australia)	338 (Europe and Australia)	49 (North and South America, Europe)
Randomization	1:1	1:1:1	Factorial: 1:1 RSG:pbo and 1:1 ramipril:pbo	Grp with inadequate control on SU: add RSG or MET, 1:1 Grp with inadequate control nn MET: add RSG or SU, 1:1	1:1:1:1 revasc+ins-prov revasc+ins-sens ins-prov alone ins-sens alone
Stratification	None	By gender	RSG results stratified for effect of ramipril, and vice versa	By background med (SU or MET)	By revasc strategy (CABG or PCI); by center

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones

	PROactive[1]	ADOPT[2]	DREAM[3]	RECORD[4]	BARI 2D[5]
Blinding	Double	Double	Double	Add-on study med is open-label; blinded adjudication of CV endpoints	Open-treatment; blinded reading of angiography
Parallel Group vs Factorial Design	Parallel	Parallel	2x2 factorial	Parallel	2x2 factorial
Patient Population	T2DM, HbA1c> ULN, history of macrovascular disease (predefined)	T2DM diagnosed ≤ 3 yrs FPG 126-240 mg/dL at scrn	Impaired glucose tolerance (FPG <126 mg/dL; 2 hr OGTT glu ≥140 and <200 mg/dL) or impaired fasting glucose (FPG ≥ 110 mg/dL and <126 mg/dL; 2 hr OGTT glu <200 mg/dL)	T2DM, inadequate control on MET or SU	T2DM with ≥50% stenosis of ≥ 2 coronary arteries; objective documentation of ischemia, or typical angina + ≥ 70% stenosis in ≥1 coronary artery
Exclusion Criteria of Particular Importance	Insulin as sole therapy for DM for ≥2 wks at any time in previous 3 months. MI, stroke, CABG or PCI in past 6 months. ACS in past 3 months. HF NYHA FC≥2. Planned CV intervention. Current TZD use.	Prior diabetes drug treatment. Unstable or severe (NYHA 3 or 4) angina. HF of any NYHA class requiring drug rx.	Prior diabetes drug treatment. CHF, history of macrovascular cardiac disease (predefined), peripheral vascular disease (predefined) or stroke	Other OHA use, dual OHA use, insulin use, prior TZD use, HF on meds	CABG or PCI in previous 12 months, HF class 3 or 4, left main coronary artery stenosis ≥50%
Study Agent Treatment(s)	Pioglitazone, force-titrated to 45 mg (added to underlying diabetes treatment[s])	RSG 4 mg up to 8 mg[6]	RSG force-titrated to 8 mg/day; ramipril, forced-titrated to 15 mg/day	Add-on RSG 4 mg up to 8 mg[7]	Medical mgmt strategy comparison: RSG or MET (titrated to max dose)[7]
Control Treatment(s)	Placebo (added to underlying diabetes treatment[s])	Metformin 500 mg up to 2000 mg Glyburide/glibenclamide 2.5 mg up to 15 mg[6]	Matching pbo RSG; matching pbo for ramipril	If on BL MET, add-on SU. If on BL SU, add-on MET.	Med mgmt strategy comparison: SU, titrated to max dose, or insulin, titrated up to 3 u/kg/day
Primary Endpoint	Time from randomization to first event in composite of: all-cause mortality; nonfatal MI (including silent); stroke; acute coronary syndrome; CABG or PCI; leg amputation above ankle; or bypass surgery or revasc in the leg	Time from randomization to monotherapy failure	Occurrence of death or diabetes (diagnostic criteria predefined)	Time to composite of CV death and/or CV hospitalization	All-cause mortality
Secondary Endpoints of Particular Relevance	Predefined: CV mortality, components of primary endpoint. Defined after trial cessation: composite of all-cause mort, nonfatal MI (excluding silent), or stroke	No predefined cardiovascular secondary endpoints	CV events composite (MI, stroke, CV death, HF, new angina, or revascularization); separate composite of MI, stroke or CV death	All cause mortality; HF; composite of all-cause mortality, MI, stroke, HF and unstable angina; time to CV death, MI, stroke and unstable angina	Composite of all-cause mortality, MI or stroke; CV mort; MI; composite of all-cause mort or MI; angina; subsequent revasc procedures

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones

	PROactive[1]	ADOPT[2]	DREAM[3]	RECORD[4]	BARI 2D[5]
Did Cardiovascular Endpoints Include Heart Failure?	No	n/a (no predefined CV endpoints)	Yes	Yes	No
Non-endpoint Cardiovascular Safety Measures	Adverse CV events	Adverse CV events	Not noted in publications	Adverse CV events	Adverse CV events
Were/Are Cardiovascular Events Adjudicated?	Yes, for endpoint events	HF adjudicated post hoc; other CV events not adjudicated	Yes, for endpoint events	Yes, for endpoint events	Yes, for cause of death, and for categorization of strokes and MIs
Were/Are Cardiovascular Events Ascertained After Cessation of Study Medication?	Yes, unless pt withdrew consent	For 30 days after last dose of study med	Yes	Yes	Not noted in materials

Abbreviations: ACS = acute coronary syndrome, BL = baseline, CABG = coronary artery bypass grafting, CHF = congestive heart failure, CV = cardiovascular, FPG = fasting plasma glucose, grp = group, GSK = GlaxoSmithKline, HF = heart failure, MET = metformin, mgmt = management, MI = myocardial infarction, mnt = maintenance, mort = mortality, n/a = not applicable, NHLBI = National Heart, Lung and Blood Institute of the National Institutes of Health, NYHA FC = New York Heart Association Functional Class, OGTT = oral glucose tolerance test, pbo = placebo, PCI = percutaneous coronary intervention, prov = providing, revasc = revascularization, RSG = rosiglitazone, sens = sensitizing, rx = treatment, scrn = screening, SU = sulfonylurea, T2DM = type 2 diabetes mellitus, TZD = thiazolidinedione

1 "PROspective PioglitAzone Clinical Trial in MacroVascular Events"; source = NDA 21073, subm 026, 24 Jan 06,

2 "A Diabetes Outcome Progression Trial", source = NDA 21071, subm 026, 28 Feb 07

3 "Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication"; sources = DREAM Investigators, 2004 and 2006

4 "Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia"; source = RECORD protocol amendment 7 (27 Feb 06), and Home 2007

5 "Bypass Angioplasty Revascularization Investigation 2 Diabetes"; source = Brooks 2006 and BARI 2D manual of operations, subm 22 May 07

6 Protocol-specified up-titration based on FPG

7 Protocol-specified up-titration based on HbA1c

ADOPT (A Diabetes Outcomes Progression Trial)

This trial, performed as a Phase 4 commitment to FDA, is the only completed long-term, prospective, controlled study of rosiglitazone for which the FDA has received a complete study report and datasets. The multidisciplinary review is ongoing; this memo will present preliminary results of the clinical review of cardiovascular safety results. Because the FDA has more complete information for this trial than for other long-term clinical trials of rosiglitazone, its cardiovascular safety findings can be presented in greater detail than can the findings of other trials, which are ongoing or have not yet been submitted.

Full Title: A Randomized, Double-Blind Study to Compare the Durability of Glucose Lowering and Preservation of Pancreatic Beta-Cell Function of Rosiglitazone Monotherapy Compared to Metformin or Glyburide/Glibenelamide in Subjects with Drug-Naïve, Recently Diagnosed Type 2 Diabetes Mellitus

Status: Complete; full study report submitted to FDA; review ongoing.

DESIGN

Objectives:

- Primary: Evaluate and compare effects of long-term monotherapy of T2DM with rosiglitazone (RSG), glyburide/glibenclamide and metformin (MET) on improvement and maintenance of glycemic control in patients with recently diagnosed T2DM. This was determined by time from randomization to monotherapy failure.
- Secondary Objective Relevant to Cardiovascular Safety: Assess long-term safety in terms of incidence of alanine aminotransferase elevations, and cardiovascular and hematological safety, in addition to changes in body weight and serum lipids.

Number of Patients: 4351 randomized. Original target sample size was 3600 patients. Due to higher than anticipated early withdrawal rate and lower than anticipated monotherapy failure rate, target sample size amended to 4182 patients.

Duration: Four years originally planned; when sample size increased, follow-up period also extended to 6 years. Mean and median followup 38.9 and 47.4 months, respectively. Total patient-years = 14,103; 4954, 4244, and 4906 for the RSG, glyburide/glibenclamide and MET groups, respectively. (Hereafter, the glyburide/glibenclamide group will be abbreviated as the SU group, although glyburide/glibenclamide represent only one subclass of sulfonylureas). Less exposure for SU group than for RSG or MET groups.

Number of Centers: 473 (North America and Europe)

Randomization: 1:1:1 randomization, with stratification by gender.

Blinding:

- Double-blind.
- Investigators and patients blinded to treatment assignment (all study medications in identical capsules).
- Bottle labels did not reveal name of drug.
- Patients blinded to dose by use of placebo during protocol-defined titration period and treatment period, so that all patients titrated up to 4 capsules/day.

- External reviewers blinded during post-study review of congestive heart failure (CHF) events.

Study Agent Treatment: Rosiglitazone, initiated at 4 mg/day, with protocol-specified up-titration to 8 mg/day possible based on fasting plasma glucose.

Controls:
- Glyburide/glibenclamide, initiated at 2.5 mg/day, with protocol-specified up-titration to as high as 15 mg/day possible based on fasting plasma glucose.
- Metformin, initiated at 500 mg/day, with protocol-specified up-titration to 2000 mg/day possible based on fasting plasma glucose.

Parallel Group Design?: yes

Patient Population: Men and women, ages 30-75 years, with type 2 diabetes diagnosed ≤ 3 years. Fasting plasma glucose 126-240 mg/dL at screening.

Exclusion Criteria of Particular Importance:
Prior diabetes drug treatment. Exceptions to this exclusion:
- Insulin use during gestational diabetes
- Short-term (≤ 1 month) insulin use to maintain glycemic control for hospitalization or medical procedure/intervention
- ≤ 2 weeks of oral hypoglycemic agent ≥ 2 weeks prior to screening, or >2 weeks-1 month of oral hypoglycemic agent ≥ 2 months prior to screening
- Congestive heart failure requiring drug therapy (any New York Heart Association [NYHA] class)
- Alanine aminotransferase (ALT) >2.5x the laboratory upper limit of normal (ULN)
- Serum creatinine >1.3 mg/dL (for men) or >1.2 mg/dL (for women)

Primary Endpoint: Time to monotherapy failure

Predefined Cardiovascular Secondary Endpoints: None

Adjudication of Cardiovascular Events: None predefined; post hoc adjudication of heart failure events

Duration of Ascertainment of Cardiovascular Events After Study Medication Cessation: 30 days

General Description of Study Conduct:
After a 4-week dietary and placebo run-in period, patients were randomized to double-blind treatment with RSG, SU or MET. Up-titration occurred based on fasting plasma glucose. For the first year of study, patients had study visits every two months; thereafter, visits occurred every three months. Fasting glucose and adverse event information were obtained at each study visit, as were other laboratory, history and physical examination data (see Tables A1 and A2 below). An oral glucose tolerance test was performed every six months. Patients remained on blinded study medication until they met criteria for monotherapy failure, which were:
- fasting plasma glucose >180 mg/dL on consecutive occasions following at least 6 weeks of dosing with the maximum tolerated dose of study medication, or
- judgment by independent adjudication committee that patient had achieved monotherapy failure.

The latter criterion was added in an amendment after it was noted that there were a number of patients who did not meet the definition of monotherapy failure in the first bullet, yet were likely to have been a monotherapy failure. These included patients who had a final FPG >180 mg/dL with no follow-up FPG, patients who did not meet the timing requirement related to maximum tolerated dose (MTD), patients for whom there was uncertainty about whether MTD had been achieved, patients withdrawn due to insufficient therapeutic effect but who did not meet the protocol definition, and patients who had been placed on combination oral or insulin therapy as a protocol violation. The independent adjudication committee included three independent physicians who were blinded to treatment assignment, and was expected to make a decision about whether such patients were actually monotherapy failures. An event would be counted as a monotherapy failure if the adjudication committee concluded that:

- it was probable that the event would have met the protocol definition of monotherapy failure, had the patient been retained in the study and if all evaluations had been performed as specified precisely by the protocol, and
- the event satisfied usual good clinical practice criteria for monotherapy failure. (Source: Adjudication Committee charter, pg 7798, ADOPT study report)

Patients who remained in study and did not have monotherapy failure had a minimum of 21 study visits and a maximum of 29 study visits. Adverse event data were routinely collected until 30 days after cessation of study medication. Patients who withdrew from treatment were asked for consent to be followed in a non-treatment observational follow-up period, which lasted until 48 months after their randomization date, but adverse event data were not routinely collected during this period (ADOPT study report, Table 2, footnote 10, pg 52).

The following tables present an abbreviated version of study procedures:

Table A1: Abbreviated Table of Study Procedures, Screening Through Year 1

	Pre-screen	Run-in Period Screen			Treatment Period			
Visit Number	**0**	**1**	**2**	**3 Baseline**	**4&5**	**6**	**7&8**	**9**
Week/Month Number	**-6 wks**	**-4 wks**	**-2 wks**	**0**	**8&16 wks**	**24 wks**	**8&10 mo**	**12 mo**
History, physical exam[1] and concomitant meds check		x	x	x	x	x	x	x
FPG	x	x	x	x	x	x	x	x
HbA1c, LFTs				x	x	x	x	x
OGTT, fasting lipids				x		x		x
Routine fasting chem, heme, urine panels; serum β-HCG		x		x		x		x
ECG		x						x
Signs/ symptoms/ adverse experiences check			x	x	x	x	x	x

Source: ADOPT study report, Table 2, pg 51
Abbreviations: β-HCG = human chorionic gonadotropin beta subunit, ECG = electrocardiogram, exam = examination, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LFTs = liver function tests, meds = medications, mo = months, OGTT = oral glucose tolerance test, wks = weeks
1 Full history and physical at visit 1; full physical exam at visit 9 also; focused interim history and physical at other visits

Table A2: Abbreviated Table of Study Proccdures, Month 15 Through Year 6

	Frequency of Procedure		
	Every 3 Months	Every 6 Months	Every 12 Months
Interim history, physical exam and concomitant meds	x		
Complete physical exam			x
FPG, HbA1c	x		
LFTs, OGTT		x	
Routine fasting chem, heme, urine panels; serum β-HCG; ECG			x
Adverse experiences check	x		

Source: ADOPT study report Tables 3 and 4, beg pg 53
Ahbreviations: β-HCG = human chorionic gonadotropin beta subunit, ECG = electrocardiogram, exam = examination, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LFTs = liver function tests, meds = medications, mo = months, OGTT = oral glucose tolerance test, wks = weeks

Once a patient met criteria for monotherapy failure, they remained in study and had adverse event data collected for 30 days after cessation of study medication.

RESULTS

Disposition:

The following table summarizes patient disposition.

Table A3: Patient Disposition in ADOPT

	RSG	SU	MET	TOTAL
Entered placebo run-in period	n/a	n/a	n/a	6385
Randomized	1456	1441	1454	4351
Withdrawn prior to first efficacy evaluation	63	104	57	224
Non-monotherapy failure withdrawals, n (%)	621 (43)	671 (47)	602 (41)	1894 (44)
Completed and monotherapy failure, n (%)	835 (57)	770 (53)	852 (59)	2457 (56)
Study-defined intention to treat (ITT) population[1]	1393	1337	1397	4127

Source: ADOPT study report, Table 6, pg 78
1 All subjects who were randomized and had at least one on-therapy value for an efficacy parameter. ITT population used for efficacy evaluation. Population of all randomized patients who received at least one dose of study medication was used for safety evaluation

A substantial percentage of patients in each treatment group discontinued treatment for reasons other than monotherapy failure. The withdrawal rate from ADOPT, both related to the endpoint of monotherapy failure, and related to other reasons, presents challenges for the interpretation of adverse event data. Methods such as expression of adverse event rates per patient year, and time-to-event analyses, were used to assist in interpretation of adverse event data in the face of differing exposure for the treatment groups.

Exposure

Mean and median durations of exposure were approximately equal for rosiglitazone and metformin, while sulfonylurea exposure was somewhat lower. Early withdrawals (within the first month of exposure) were more common among sulfonylurea group patients; this excess was primarily due to hypoglycemia. Lower exposure for SU group patients was important in assessing event rates, as it might bias rates in favor of SU over RSG or MET.

Table A4: Duration of Exposure (All Randomized Patients)

Exposure Interval		Number of Subjects, n (%)			
Days	Months[1]	RSG N=1456	GLY/GLIB N=1441	MET N=1454	Total N=4351
≤ 28	≤1	42 (2.9)	78 (5.4)	34 (2.3)	154 (3.5)
29-90	1-3	59 (4.1)	71 (4.9)	58 (4.0)	188 (4.3)
91-180	3-6	61 (4.2)	58 (4.0)	59 (4.1)	178 (4.1)
181-270	6-9	51 (3.5)	57 (4.0)	61 (4.2)	169 (3.9)
271-360	9-12	38 (2.6)	66 (4.6)	37 (2.5)	141 (3.2)
361-540	12-18	57 (3.9)	72 (5.0)	67 (4.6)	196 (4.5)
541-720	18-24	72 (4.9)	79 (5.5)	64 (4.4)	215 (4.9)
721-1080	24-36	117 (8.0)	177 (12.3)	123 (8.5)	417 (9.6)
1081-1440	36-48	146 (10.0)	179 (12.4)	163 (11.2)	488 (11.2)
>1440	>48	813 (55.8)	604 (41.9)	788 (54.2)	2205 (50.7)
Mean (Days) ±SD		1242.7±652.5	1075.6±664.8	1232.3±646.9	1183.9±659.1
Median		1463.0	1217.0	1459.0	1443.0
Range		1-2189	1-2214	1-2203	1-2214

1. Approximation
Data Source: Table 6.7.1

Source: ADOPT study report, Table 47, pg 154

Demographic and Other Baseline Characteristics

In general, baseline and demographic characteristics were similar among treatment groups. Patients in the sulfonylurea group were slightly numerically less likely to be smokers. Patients in the metformin group were slightly numerically more likely to test positive for antibodies to glutamic acid decarboxylase. Patients in the rosiglitazone group were slightly numerically less likely to have a history of cardiovascular disease. None of these differences between groups was statistically significant. Mean waist:hip ratio was very slightly numerically lower in the sulfonylurea group (0.94 SU vs 0.95 for RSG and MET), with a p-value for the difference of 0.0974.

Table A5: Summary of Demographic and Other Baseline Characteristics, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Characteristic	Category	RSG N=1456	SU N=1441	MET N=1454	TOTAL N=4351	p-value
Gender, % male	% male	55.7	58.0	59.4	57.5	0.1218
Age, mean (SD), years		56.3 (9.99)	56.4 (10.20)	56.9 (9.34)	56.5 (10.05)	0.2892[1]
Race, %	White	87.2	89.0	89.1	88.5	0.2326
	Black	4.2	4.2	3.7	4.0	
	Asian	2.7	2.2	2.4	2.4	
	Hispanic	5.2	4.2	3.8	4.4	
	Other	0.7	0.3	1.0	0.6	
Country, %	USA	37.8	38.4	38.0	38.1	1.0000

Table A5: Summary of Demographic and Other Baseline Characteristics, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Characteristic	Category	RSG N=1456	SU N=1441	MET N=1454	TOTAL N=4351	p-value
	Canada	14.2	14.2	14.2	14.2	
	France	9.1	8.7	9.0	9.0	
	Germany	10.8	10.6	11.1	10.8	
	United Kingdom	7.3	7.6	7.2	7.4	
	Spain	9.1	9.3	9.2	9.2	
	Other	11.1	11.1	11.4	11.4	
BMI, kg/m^2 (SD)		32.2 (6.69)	32.2 (6.27)	32.1 (6.05)	32.2 (6.34)	0.9741[1]
Weight, kg (SD)		91.5 (19.68)	92.0 (19.99)	91.6 (18.67)	91.7 (19.45)	0.9157[1]
Ratio of waist:hip circumference, cm/cm, mean (SD)		0.95 (0.091)	0.94 (0.086)	0.95 (0.096)	0.95 (0.091)	0.0974[1]
Smoker, %		15.5	13.3	15.0	14.6	0.2167
Alcohol consumers, %		46.2	44.9	45.6	45.5	0.7816
Glutamic acid decarboxylase antibody positive, %		4.0	3.6	5.1	4.2	0.1462
Duration of diabetes, %	<1 yr	44.7	44.2	46.3	45.1	0.3639
	1 yr	34.1	33.4	31.9	33.1	
	2 yrs	18.0	18.7	17.9	18.2	
	3 yrs	3.0	3.3	3.6	3.3	
	≥ 4 yrs	0.3	0.4	0.3	0.3	
Hypertension[2] present, % of patients		72.9	72.9	72.8	72.9	0.9978
On hypertension med(s), % of patients		51.1	53.3	50.7	51.3	0.6822
Diastolic BP, mmHg, mean (SD)		79.8 (8.67)	79.3 (8.96)	79.7 (8.92)	79.6 (8.85)	0.4837[1]
Systolic BP, mmHg, mean (SD)		133.0 (15.66)	132.7 (15.40)	132.8 (15.45)	132.9 (15.50)	0.8313[1]
Dyslipidemia[3] present, % of patients		66.3	63.9	66.0	65.4	0.3500
On dyslipidemia treatment, % of patients		26.0	25.7	25.9	25.9	0.9819
Medical history of CV disease[4], % of patients		15.9	17.1	18.5	17.2	0.1692

Source: ADOPT study report, Tables 13 and 14, beg pg 93
1 Kruskall-Wallis test; other p-values by chi-squared test
2 Hypertension defined as systolic BP ≥ 130 mm HG or diastolic BP ≥ 85 mmHg, or medical history of hypertension
3 Dyslipidemia defined as HDL <40 mg/dL for men, HDL <50 mg/dL for women, or TG ≥ 150 mg/dL
4 CV medical history = presence of any of a set of defined terms for myocardial ischemia, heart failure, arrhythmia and other CV conditions; list of conditions begins pg 2458, ADOPT study report

Baseline cardiovascular medication use was similar among treatment groups. A total of 24% of patients in each treatment group were taking angiotensin converting enzyme inhibitors. Nitrate use was low at baseline, with 2%, 3% and 3% of patients taking nitrates in the RSG, SU and MET groups, respectively. Angina requiring continual nitrate treatment was an exclusion criterion.

Primary endpoint

The focus of this briefing document is the cardiovascular safety of rosiglitazone, and therefore a detailed review of the efficacy findings will not be presented.

The primary efficacy endpoint was the time from randomization to monotherapy failure.

Monotherapy failure was defined as either:

- fasting plasma glucose of >180 mg/dL on consecutive occasions following at least 6 weeks of dosing with the maximum tolerated dose of the study medication, or
- for patients who failed to meet the above criterion, judgment by the independent adjudication committee that monotherapy failure had occurred (see section entitled *General Description of Study Conduct* above).

The following table and Kaplan-Meier curves present the applicant's analyses of the primary endpoint:

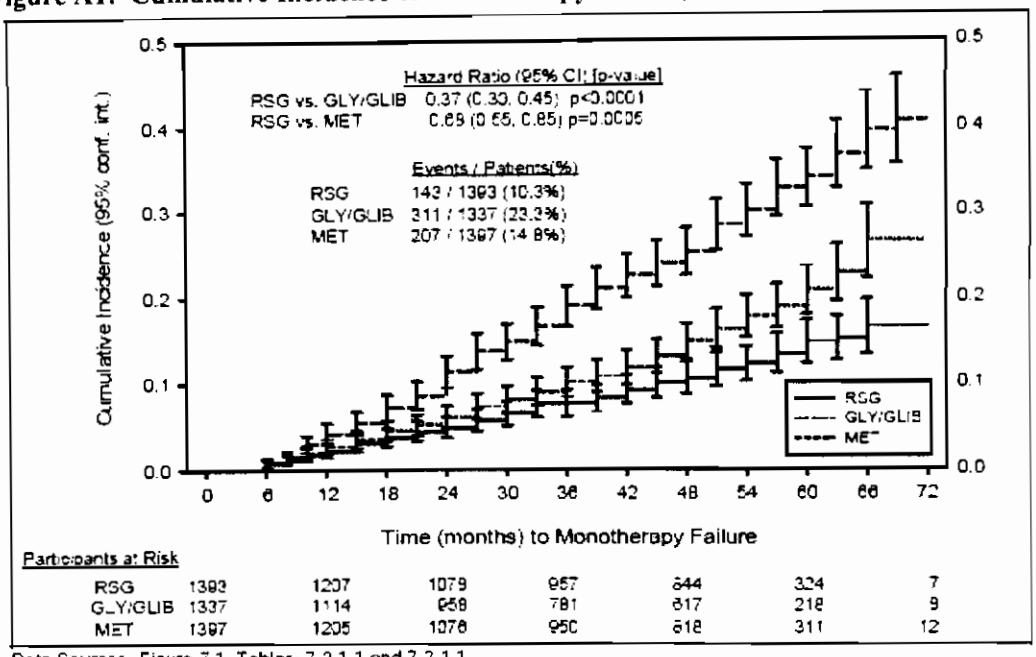
Table A6: Analysis of Time to Monotherapy Failure, Intention-to-Treat Population

	RSG N=1393	GLY/GLIB N=1337	MET N=1397
Number of subjects with event	143	311	207
Cumulative incidence (95% CI) at 5 years	0.15 (0.12, 0.17)	0.34 (0.30, 0.37)	0.21 (0.18, 0.24)
RSG vs Control			
Hazard ratio (95% CI)[1]		0.37 (0.30, 0.45)	0.68 (0.55, 0.85)
p value		<0.0001	0.0005

1. Hazard ratios reflect the ratio of the RSG hazard rate to the control treatment hazard rates. A hazard ratio less than one indicates that rate to event occurrence is slower for RSG relative to control.
Data Source: Table 7.3.1.1 and Table 7.2.1.1

Source: ADOPT study report, Table 21, pg 109

Figure A1: Cumulative Incidence of Monotherapy Failure, Intention-to-Treat Population



Data Sources: Figure 7.1. Tables: 7.2.1.1 and 7.3.1.1.

Source: ADOPT study report, Figure 11, pg 110

By these analyses, rosiglitazone was associated with a lower rate of monotherapy failure (by specified criteria) over time than was metformin or glyburide/glibenclamide.

Multiple secondary endpoints were also analyzed, but are not included in the focus of this briefing document.

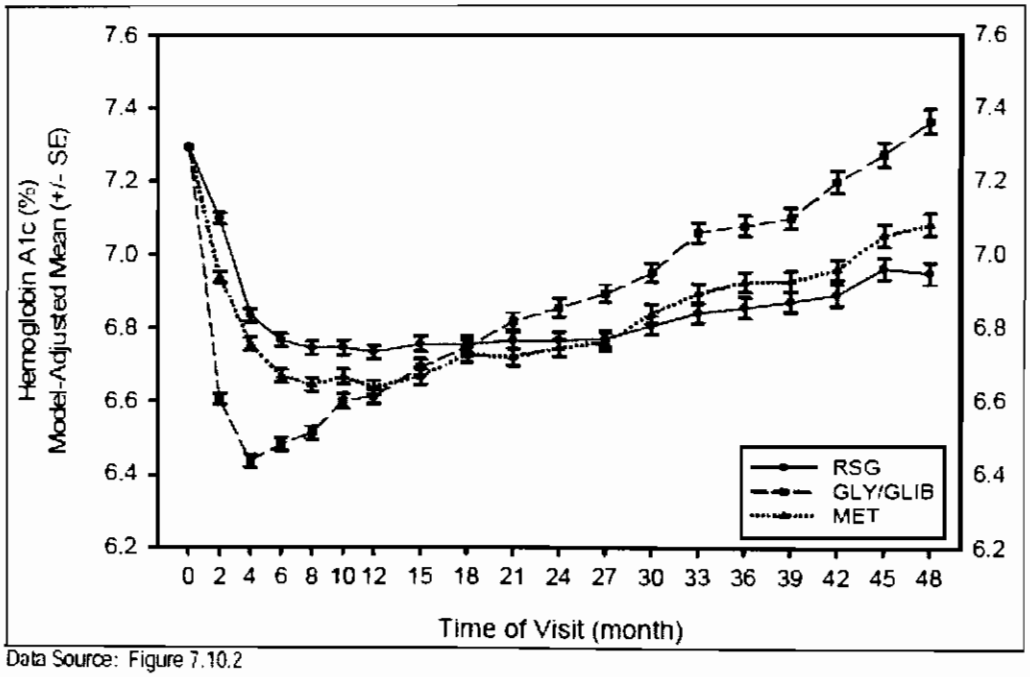
Hemoglobin A1c, Lipids and Blood Pressure at Endpoint

When examining cardiovascular safety, differences in cardiovascular risk factors between treatment groups over the course of study can complicate interpretation. In an ideal setting, values for risk factors such as blood sugar, lipids and blood pressure would be equal between treatment groups over time. In some trials (such as the ongoing BARI 2D trial), active management of cardiovascular risk factors occurs, with the goal of achieving equal control between groups; this facilitates a better estimate of cardiovascular risk or benefit. Other trials (such as PROactive) have been complicated by differences in risk factor values at endpoint, leading to discussion regarding whether any positive benefits were simply due to risk factor changes, with the possibility that, risk factors being equal, there would have been no demonstrable effect of the drug. Therefore, risk factors were also examined in the review of ADOPT.

Because RSG was assoeiated with fewer monotherapy failures than SU or RSG, one might logically expeet lower hemoglobin A1c (HbA1c) among RSG-treated patients than among patients in the MET and SU groups. Analyses of HbA1c were complieated by withdrawals due to monotherapy failure. In the first year of therapy, mean HbA1c was lower in the sulfonylurea group than in the other two groups, and HbA1c in the metformin group was somewhat lower than HbA1c in the rosiglitazone group. Over time, HbA1c in the RSG group became lower than that in either group. It seems that this would be expected, as more patients in the SU and MET groups

began to have high blood sugars that led to monotherapy withdrawal; these high blood sugars would likely have been associated with higher HbA1cs. GSK performed analyses using multiple models; results were qualitatively similar.

Figure A2: Model-Adjusted Mean HbA1c (%) Values by Visit to 48 Months, ITT Population



Data Source: Figure 7.10.2

Source: ADOPT study report, Figure 19, pg 118. Model described on pg 73; multivariate linear model incorporating on-therapy values at all time points up to 48 months. Model incorporated effects for baseline, country group, treatment, gender, time and treatment-time interaction.

Low density lipoprotein cholesterol (LDL) increased in the RSG group over the first 6 months of study, and then declined until end of study. In the SU and MET groups, LDL declined gradually throughout study. At 48 months, LDL was statistically significantly higher in the RSG group than in the other treatment groups.

Table A7: Multivariate Linear Model Analysis of Log-Transformed Low Density Lipoprotein Cholesterol (mg/dL)

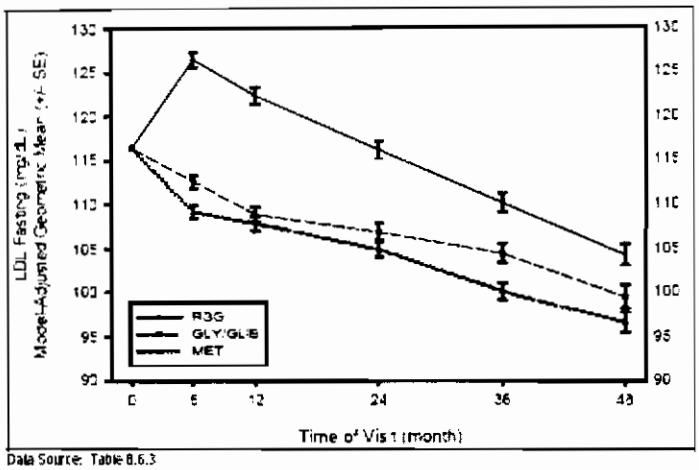
	RSG N=1456	GLY/GLIB N=1441	MET N=1454
LDL Cholesterol , n[1]	1186	1174	1215
Baseline, Geometric mean (CV%[2]) mg/dL	116.9 (30.9)	116.1 (33.5)	116.3 (30.1)
Baseline, Geometric mean (CV%[2]) mmol/L	3.0403 (30.9)	3.0175 (33.5)	3.0248 (30.1)
% Change from Baseline to 48 Months			
Adjusted Mean (%) (95% CI)	-10.5 (-12.5, -8.4)	-14.6 (-16.7, -12.4)	-17.0 (-18.9, -15.1)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%) (95% CI) p-value		4.8 (1.4, 8.4) 0.0059	7.9 (4.5, 11.4) <0.0001

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Data Source: Table 8.11.1

Source: ADOPT study report, Table 113, pg 246

Figure A3: Model-Adjusted Geometric Mean LDL Cholesterol (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.6.3

Source: ADOPT study report, Figure 73, pg 246

High-density lipoprotein (HDL) cholesterol increased over time in all three treatment groups. The increase from baseline to 48 months was greater for the RSG group than for either of the other treatment groups.

Table A8: Multivariate Linear Model Analysis of Log-Transformed High Density Lipoprotein Cholesterol (mg/dL), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

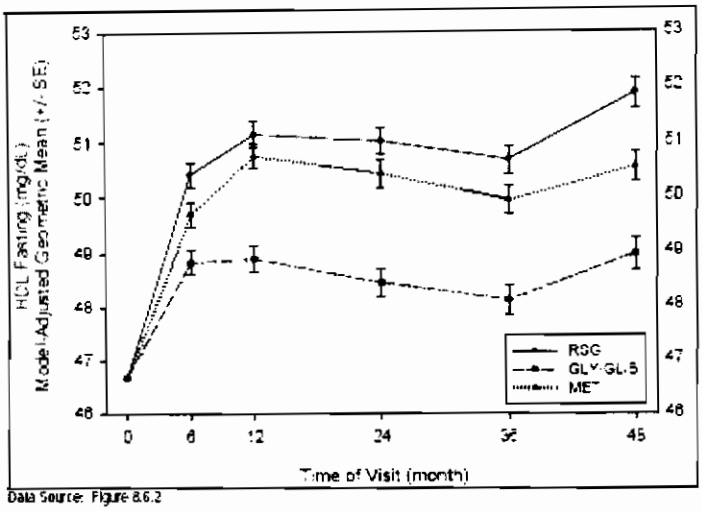
	RSG N=1456	GLY/GLIB N=1441	MET N=1454
HDL Cholesterol , n[1]	1281	1231	1296
Baseline, Geometric mean (CV%[2]) mg/dL	46.4 (24.8)	46.6 (25.3)	46.6 (24.9)
Baseline, Geometric mean (CV%[2]) mmol/L	1.2064 (24.8)	1.2128 (25.3)	1.2128 (24.9)
% Change from Baseline to 48 Months			
Adjusted Mean (%) (95% CI)	11.1 (10.0, 12.3)	4.9 (3.6, 6.1)	8.2 (7.1, 9.4)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%) (95% CI) p-value		6.0 (4.4, 7.6) <0.0001	2.7 (1.2, 4.2) 0.0004

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Data Source: Table 8.11.1

Source: ADOPT study report, Table 112, pg 245

Figure A4: Model-Adjusted Geometric Mean HDL (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Figure 8.6.2

Source: ADOPT study report, Figure 72, pg 244

Triglyceride (TG) levels increased in the RSG group over the first 6 months of study, then declined throughout the rest of study. In the SU and MET groups, TG levels declined over the first 6 months of study, and gradually increased over the remainder of study. At 48 months, TG levels were statistically significantly lower in the RSG group than in the SU group, although the absolute difference was small and may not be clinically meaningful. There was no significant difference in TG levels at 48 months when comparing RSG to MET.

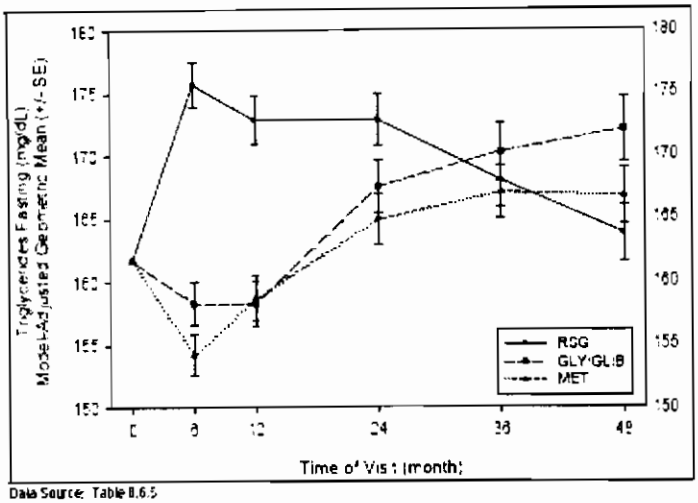
Table A9: Multivariate Linear Model Analysis of Log-Transformed Triglycerides, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

	RSG N=1456	GLY/GLIS N=1441	MET N=1456
Triglycerides; n[1]	1286	1240	1296
Baseline, Geometric mean (CV[2]%[3]) mg/dL	165.9 (59.3)	160.2 (57.8)	165.5 (60.0)
Baseline, Geometric mean (CV[2]%[3]) mmol/L	1.8741 (59.3)	1.18103 (57.8)	1.8697 (60.0)
% Change from Baseline to 48 Months			
Adjusted Mean (%) (95% CI)	1.3 (-1.4, 4.0)	6.4 (3.3, 9.6)	3.1 (0.4, 5.9)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%) (95% CI) p-value		-4.8 (-8.4, -1.0) 0.0131	-1.8 (-5.3, 1.9) 0.3433

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Source: ADOPT study report, Table 114, pg 248

Figure A5: Model-Adjusted Geometric Mean Triglycerides (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.6.5

Source: ADOPT study report, Figure 74, pg 247

Mean systolic blood pressure declined slightly in the RSG group over time, while rising slightly in the MET and SU treatment groups. The difference in this change from baseline to 48 months was statistically significant for the RSG vs SU comparison (no adjustment for multiple comparisons), but not for the RSG vs MET comparison.

Table A10: Multivariate Linear Model Analysis of Change from Baseline in Systolic Blood Pressure (mmHg), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Systolic Blood Pressure	RSG N=1456	GLY'GLIB N=1441	MET N=1454
Number of subjects with event	1394	1331	1397
Mean±SD at Baseline	132.8±15.53	132.8±15.40	132.8±15.54
Change from Baseline to 48 Months ±SE	-0.8±0.47	1.1±0.50	0.3±0.47
95% CI	-1.8, 0.1	0.0, 2.1	-0.6, 1.2
RSG vs. Control			
Adjusted Mean Difference (95% CI)		-1.9 (-3.3, -0.6)	-1.1 (-2.4, 0.1)
p-value		0.0058	0.0831

Data Source: Table 8.6.5

Source: ADOPT study report, Table 104, pg 229

Mean diastolic blood pressure declined slightly in all 3 treatment groups over time; the decline from baseline to 48 months was statistically significantly greater in the RSG group compared to the other two treatment groups.

Table A11: Multivariate Linear Model Analysis of Change from Baseline in Diastolic Blood Pressure (mmHg), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Diastolic Blood Pressure	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Number of subjects with event	1394	1331	1397
Mean±SD at Baseline	79.7±8.60	79.3±8.94	79.8±8.95
Change from Baseline to 48 Months ±SE 95% CI	-3.1±0.29 -3.6, -2.5	-1.0±0.33 -1.7, -0.4	-1.6±0.29 -2.2, -1.1
RSG vs. Control Adjusted Mean Difference (95% CI) p-value		-2.0 (-2.9, -1.2) <0.0001	-1.4 (-2.2, -0.6) 0.0004

Data Source: Table 8.6.5

Source: ADOPT study report, Table 105, pg 229

These differences in risk factors at endpoint were generally slightly favorable for RSG, except for LDL cholesterol, which was unfavorably higher for RSG. The expected difference in CV risk associated with these changes is diffieult to quantify, although there are some models which have been employed, such as a UKPDS-based model which was used for a published post hoc evaluation of the PROactive data, and which suggested that most of the numerically favorable cardiovascular risk reduction for pioglitazone could be accounted for by changes in risk factors (Holman 2006). Data for UKPDS have never been submitted to the FDA, although the FDA requested the data, and therefore the FDA cannot verify the validity of this model. The UKPDS was not conducted under a U.S. IND and was not sponsored by a pharmaceutical company, but rather by the UKPDS study group. A cardiovascular event rate model based on modification of CV risk factors has not yet been employed for the ADOPT risk factor data. Some uncertainty remains about the contribution of differential risk factor results to expeeted CV event risk in ADOPT.

Deaths

A total of 96 deaths were reported. Of these, 48 occurred during treatment or within 30 days of cessation of treatment. There were 21 deaths that occurred more than 30 days after cessation of treatment, but were due to an adverse event that occurred on treatment or within 30 days of cessation of treatment. There were 27 deaths that occurred more than 30 days after cessation of treatment and were due to an adverse event that also occurred more than 30 days after eessation of treatment. Adverse events were captured until 30 days after cessation of treatment, but were not routinely captured after that. Therefore, data for deaths and other adverse events occurring more than 30 days after cessation of treatment are possibly ineomplete.

The following table summarizes the numbers of reported deaths in each of the treatment groups.

Table A12: Summary of Deaths Occurring On-therapy and Post-therapy, Population of All Patients Who Received at Least One Dose of Study Medication

	RSG N=1456 PY[1]=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	# Deaths/ 100 PY	n (%)	# Deaths/ 100 PY	n (%)	# Deaths/ 100 PY
Total Deaths	34 (2.3)	0.7	31 (2.2)	0.7	31 (2.1)	0.6
Deaths occurring on treatment or within 30 days of cessation of treatment	12 (0.8)	0.2	21 (1.5)	0.5	15 (1.0)	0.3
Deaths occurring >30 days after cessation of treatment, but due to an event that had onset during treatment or within 30 days of cessation of treatment	11 (0.8)	0.2	6 (0.4)	0.1	4 (0.3)	0.1
Deaths occurring >30 days after cessation of treatment, and due to event that occurred >30 days after cessation of treatment	11 (0.8)	0.2	4 (0.3)	0.1	12 (0.8)	0.2

Source: ADOPT study report Table 1697, pg 6619
1 Patient-years on treatment

The following tables list each of these deaths; the clinical reviewer examined each death narrative (unblinded) to assess for appropriateness of assignment of cause of death.

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
040-80119	RSG	64	f	181	181	181	Road traffic accident	Injuries from motor vehicle accident	Same as reported cause
189-81714	RSG	65	f	917	917	917	Myocardial infarction	Sudden death myocardial infarction	Sudden death with possible MI per later report by primary care physician; no description of event; no autopsy
306-82363	RSG	66	m	872	281	873	Prostate cancer	Prostate cancer (terminal phase)	Same
313-82618	RSG	68	m	884	882	885	Myocardial infarction	Myocardial infarction	Sudden death; probable MI (sudden collapse in street, preceded 3 days earlier by precordial pain)
315-83636	RSG	66	m	995	508	1022	Esophageal carcinoma	Hepatorenal insufficiency due to esophageal cancer	Hepatorenal failure due to esophageal cancer with hepatic metastases
324-82710	RSG	54	m	1009	1009	1009	Drowning	Drowning	Same
405-80736	RSG	72	m	81	82	82	Cardiac failure acute	Acute heart failure	"Acute heart failure" with no prior symptoms; no description of symptoms and no autopsy
537-81012	RSG	59	m	45	64	64	Ventricular fibrillation	Ventricular fibrillation	Same
792-25702	RSG	33	m	1380	1381	1382	Cerebrovascular accident	Apoplexy	Cerebrovascular accident
792-26191	RSG	53	m	61	62	62	Cardiac failure acute	Acute heart failure	Probable acute heart failure; symptoms not described
841-91751	RSG	71	m	634	568	649	Abdominal neoplasm	Neoplasia intra-abdominal	Same
844-22604	RSG	55	m	368	298	374	Colon cancer	Sigmoid colon adenocarcinoma PT3PN1 with hepatic and peritoneal metastases	Same
137-79184	SU	56	m	1038	1066	1066	Death (sic)	Unknown	Possible hypoglycemia; found on floor in asystole with BG 20
204-22661	SU	69	m	124	55	145	Metastases to abdominal cavity	Disseminated cancer (primary cancer unknown)	Metastatic cancer of unknown primary
204-83418	SU	70	m	1555	1569	1575	Cardiac arrest/ cardiac failure	Heart failure and cardiac arrest	Heart failure with subsequent in-hospital cardiac arrest

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
206-82233	SU	74	f	1861	1862	1887	Diabetic complication	Diabetic complications	In-hospital death after hypoglycemic coma, renal failure, and multiple recent partial lower extremity amputation procedures
207-82244	SU	71	m	27	43	48	Cerebral ischemia	Cerebral anoxemia due to cardiac arrest	Cardiac arrest with probable cerebral anoxia; death 7 days later
234-23558	SU	64	m	303	323	323	Arrhythmia	Myocardial ischemia and secondary arrhythmia	Arrhythmia per autopsy
234-26868	SU	69	f	116	117	117	Subarachnoid hemorrhage	Subarachnoid hemorrhage	Same
276-83292	SU	65	m	34	35	36	Myocardial infarction	Myocardial infarction but waiting for autopsy	Myocardial infarction
280-78680	SU	57	m	858	860	860	Myocardial infarction	Myocardial infarction	Myocardial infarction with asystole
283-78672	SU	72	f	901	901	904	Myocardial infarction/ pulmonary edema	Anterior myocardial infarction, cardiogenic shock, no death certificate available, death summary only	Anterior myocardial infarction
284-83321	SU	61	m	336	273	336	Epiglottic carcinoma	Hemorrhage of the pharynx	Pharyngeal hemorrhage due to epiglottic cancer
327-80905	SU	55	m	496	497	497	Completed suicide	Suicide	Same
328-80909	SU	56	m	114	114	114	Road traffic accident	Public way accident	Motor vehicle accident
338-80859	SU	70	m	941	942	942	Sudden death	Cause unknown, possible pulmonary embolism or massive myocardial infarction	Sudden death shortly after episode of chest discomfort and dyspnea
424-80648	SU	55	m	826	847	847	Respiratory failure	Respiratory insufficiency	Ventricular fibrillation with hypoxic brain damage followed by pneumonia and respiratory failure
474-91315	SU	68	f	1230	1231	1243	Pneumonia	Pneumonia	Same
705-81122	SU	74	m	1282	1287	1287	Myocardial infarction	Myocardial infarction	Same
797-25790	SU	75	f	326	326	328	Cerebrovascular accident	Apoplexia	Same

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
811-22102	SU	74	m	1295	1296	1296	Cerebrovascular accident	Probable acute stroke	Same
906-80462	SU	70	m	372	377	379	Cardiac arrest/ pulmonary edema	Pulmonary embolus	Pulmonary embolus after stroke
964-80531	SU	73	f	1192	1140	1198	Metastases to liver	Liver metastatic disease	Metastatic colon cancer
030-79292	MET	56	m	260	275	275	Pulmonary embolism	Cardiac arrest, pulmonary embolus, status post coronary artery bypass	Probable pulmonary embolus
077-79927	MET	67	m	978	952	987	Lung neoplasm malignant	Metastatic squamous cell cancer of lung	Same
183-81863	MET	69	m	553	554	577	Pancreatic mass	Pancreatic mass	Pancreatic cancer
196-82164	MET	68	m	1443	1443	1447	Cerebrovascular accident	Massive stroke	Same
232-23582	MET	56	m	433	434	434	Cardiac arrest	Cardiac arrest	Sudden out-of-hospital death
278-26729	MET	62	m	1111	575	1125	Brain neoplasm	Cancerous brain tumor	Same
324-82709	MET	69	m	770	770	770	Aortic dissection	Aortic dissection	Same
403-82416	MET	64	m	954	954	954	Crushing injury of trunk	Car accident	Same
455-82445	MET	72	f	571	571	571	Cerebral infarction	Cerebral infarction with left hemiplegia	Same
498-82456	MET	75	m	811	812	831	Cardiac failure	Sepsis	Heart failure
691-91348	MET	66	f	154	154	167	Esophageal varices hemorrhage	Esophagus varicose vein bleeding	Same
792-28149	MET	71	m	539	549	549	Circulatory collapse	Cardiovascular breakdown	Sudden in-hospital death after rib fracture complicated by pneumonia
807-81209	MET	51	m	104	104	104	Cardiac arrest	Cardiac arrest	Same
952-80532	MET	67	m	245	245	245	Myocardial ischemia	Acute myocardial ischemia	Sudden death with autopsy report of acute myocardial ischemia

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
956-90891	MET	55	m	1348	1316	1348	Abdominal sepsis	Acute respiratory distress syndrome (pulmonary edema, pneumonia, lung collapse) due to intra-abdominal sepsis	Acute respiratory distress after postoperative intra-abdominal infection

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted the numbers of cardiovascular deaths which occurred within 30 days of cessation of study medication, and broke down the total number by subcategories of CV death.

Table A14: Numbers of Cardiovascular Deaths Which Occurred During Treatmcnt or Within 30 Days of Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Ratc/ 100 PY
Any cardiovascular cause	6 (0.41)	0.12	13 (0.90)	0.31	8 (0.55)	0.16
Myocardial ischemia likely (includes sudden unexplained deaths)	2 (0.14)	0.04	6 (0.42)	0.14	3 (0.21)	0.06
Cerebrovascular	1 (0.07)	0.02	4 (0.28)	0.09	2 (0.14)	0.04
Heart failure	2 (0.14)	0.04	1 (0.07)	0.02	1 (0.07)	0.02
Arrhythmia	1 (0.07)	0.02	2 (0.14)	0.05	0	n/a
Other	0	n/a	0	n/a	2 (0.14)	0.04
Non-heart-failure cardiovascular	4 (0.27)	0.08	12 (0.83)	0.28	7 (0.48)	0.14

Source: Table A13 above

From these numbers, it does not appear that RSG was associated with a higher incidence of overall CV death, or of death from a particular category of cardiovascular cause. The total number of cardiovascular deaths is small, which limits conclusions. The post hoc and unblinded nature of the clinical reviewer's assessment of cause of death is also subject to bias, although every effort at objectivity was made.

These numbers of cardiovascular deaths may vary from those identified by GSK in their post hoc analyses of MACE endpoints; in those analyses, non-CHF deaths were included, and were identified as deaths occurring due to an SAE that had a MedDRA Lower Level Term within the set of non-CHF cardiovascular events that were prespecified for the ADOPT CV event groupings (source, NDA 21071 SE8 022, 31 May 07 submission, pages 52-77).

Table A15: Listing of Deaths Occurring >30 Days After Cessation of Treatment, but Due to an Adverse Event that Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
234-26873	RSG	55	m	47	12	726	Sarcoma	Sarcoma with pulmonary metastases	Same
236-26763	RSG	56	m	675	675	720	Adenocarcinoma	Metastatic adenocarcinoma of unknown etiology	Same
293-83158	RSG	58	f	506	409	595	Pancreatic carcinoma	Pancreatic carcinoma	Same
316-80901	RSG	68	f	979	974	1030	Rectal cancer	Terminal evolution of rectal adenocarcinoma	Metastatic rectal adenocarcinoma
324-83746	RSG	65	f	1001	973	1203	Metastases to liver	Liver metastases	Metastatic carcinoma of unknown primary
336-82286	RSG	47	f	819	820	1067	Pancreatic carcinoma metastatic	Primary cancer of the pancreas	Metastatic pancreatic carcinoma
431-82443	RSG	68	m	704	698	745	Gastric cancer	Gastric cancer	Same
455-82501	RSG	70	m	83	33	285	Lung neoplasm malignant	Lung cancer	Same
499-22765	RSG	69	m	1392	1377	1430	Hepatic neoplasm malignant	Organ failure due to cancer progression	Hepatocellular carcinoma
816-91795	RSG	67	m	647	623	681	Lung adenocarcinoma	Lung adenocarcinoma	Same
925-82775	RSG	70	m	163	65	324	Pancreatic carcinoma	Carcinoma pancreas	Same
232-23579	SU	75	m	1440	1441	1602	Subarachnoid hemorrhage	Respiratory failure	Subarachnoid hemorrhage
306-25732	SU	73	m	211	203	269	Metastases to liver	Liver metastases	Metastatic cancer, possibly of pancreatic primary
315-82636	SU	46	m	370	252	543	Gastric cancer	Stomach adenocarcinoma	Gastric adenocarcinoma
896-22952	SU	72	m	511	533	767	Renal cell carcinoma stage unspecified	Renal cancer	Same
917-26409	SU	74	m	190	161	451	Lung neoplasm malignant	Malignant neoplasm of lung	Same
957-90922	SU	66	m	1824	1842	1916	Lung cancer metastatic	Lung cancer with brain + liver secondaries (sic)	Metastatic lung cancer
302-25723	MET	73	m	441	442	509	Small intestine carcinoma	Complication of digestive surgery (high occlusion by cancer)	Enteral hemorrhage after surgery for small intestine carcinoma

Table A15: Listing of Deaths Occurring >30 Days After Cessation of Treatment, but Due to an Adverse Event that Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
321-83732	MET	64	m	869	868	1088	Gastric cancer	"Epidermmoide carcinoma oesophage with ganglionnar and pulmonary development" (sic)	Gastric cancer
442-91285	MET	61	f	30	16	108	Glioblastoma multiforme	Glioblastoma multiforme right frontal	Same
829-91261	MET	74	m	469	464	507	Adenocarcinoma	Cardiorespiratory arrest due to adenocarcinoma	Metastatic adenocarcinoma of unknown primary

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted one cardiovascular death which occurred more than 30 days of cessation of study medication, but was due to an adverse event which had its during study treatment or <30 days after cessation of study treatment.

Table A16: Cardiovascular Death Which Occurred More than 30 Days After Cessation of Treatment, but Was Due to An Adverse Event Which Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Any cardiovascular cause	0	n/a	1 (0.07)	0.02	0	n/a
Cerebrovascular	0	n/a	1 (0.07)	0.02	0	n/a
Non-heart-failure cardiovascular	0	n/a	1 (0.07)	0.02	0	n/a

Source: Table A15 above

The majority of all deaths which fell into this time category were due to malignancies. There was one cerebrovascular death in the SU group, but no other cardiovascular deaths.

Table A17: Listing of Deaths Occurring >30 Days after Cessation of Treatment and Due to an Adverse Event that Had Its Onset >30 Days after Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
077-79370	RSG	54	m	626	1410	1410	not assigned	Cardiac arrest	No death narrative
135-81418	RSG	45	m	372	712	712	not assigned	Cancer, type unknown	No death narrative
176-24748	RSG	66	m	1010	1088	1088	Pulmonary embolism	Pulmonary embolism	Probable pulmonary embolism
176-79764	RSG	63	m	1372	1424	1424	Road traffic accident	Motor vehicle accident	Motor vehicle accident; possible suicide
240-21895	RSG	56	m	1006	1053	1053	Cardiac disorder	Atherosclerotic coronary artery disease	"Widespread heart disease"
442-91283	RSG	68	m	1	41	41	Death (sic)	Reason unknown; no autopsy	Death of unknown cause; study medication not found
610-83483	RSG	73	f	785	1549	1549	not assigned	Died in fire	No death narrative
792-80721	RSG	60	m	435	1278	1278	Myocardial infarction	Myocardial infarction	Probable myocardial infarction
804-22579	RSG	54	m	139	1453	1453	not assigned	Respiratory failure secondary to respiratory infeetion related to amyotrophic lateral sclerosis	No death narrative
822-22348	RSG	66	m	22	553	1154	Lung neoplasm malignant	Lung eancer	Same
842-91764	RSG	66	m	17	871	871	not assigned	Suicide	No death narrative
034-78765	SU	59	m	968	1035	1035	not assigned	Cerebrovascular accident	No death narrative
180-81962	SU	71	m	246	1454	1454	not assigned	Cancer	No death narrative
256-91028	SU	61	m	1113	1664	1664	not assigned	Subdural haemotoly (sic)	No death narrative
902-22752	SU	49	f	43	502	502	not assigned	Cancer of pancreas with metastases	No death narrative
075-81378	MET	70	m	1	544	544	not assigned	Hepatic failure	No death narrative

Table A17: Listing of Deaths Occurring >30 Days after Cessation of Treatment and Due to an Adverse Event that Had Its Onset >30 Days after Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
153-78609	MET	59	m	1457	1520	1520	Sudden cardiac death	Sudden cardiac death	Same
179-79818	MET	65	m	211	315	316	Cardiac failure	Heart failure	Same
331-25762	MET	68	m	12	702	702	not assigned	Suicide	No death narrative
331-82582	MET	65	f	998	1653	1653	not assigned	Stroke	No death narrative
403-82449	MET	69	m	502	546	546	Myocardial infarction	Heart infarction	Myocardial infarction
432-80822	MET	51	m	51	1407	1407	not assigned	Heart failure	No death narrative
702-81106	MET	74	m	1477	1768	1768	Arteriosclerosis coronary artery	Heart disease	"Heart disease" on autopsy; found dead
792-26159	MET	56	f	141	495	495	not assigned	Cardiovascular system failure	No death narrative
792-91361	MET	46	m	473	657	657	not assigned	Hyperosmeslatic (sic) coma	No death narrative
841-22181	MET	63	m	174	1123	1123	not assigned	Head pancreas adenocarcinoma	No death narrative
843-91647	MET	41	m	309	923	923	not assigned	Car accident	No death narrative

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted the numbers of cardiovascular deaths which occurred more than 30 days after cessation of study medication, and which were due to an event which had its onset more than 30 days after cessation of study medication. The total number of these cardiovascular deaths was then broken down by subcategories of CV death.

Table A18: Numbers of Cardiovascular Deaths Which Occurred More Than 30 Days after Cessation of Treatment, and Which Were Due to an Event Which Had Its Onset More Than 30 Days After Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Any cardiovascular cause	4 (0.27)	0.08	2 (0.14)	0.05	7 (0.48)	0.14
Myocardial ischemia likely (includes sudden unexplained deaths)	4 (0.27)	0.08	0	n/a	3 (0.21)	0.06
Cerebrovascular	0	n/a	2 (0.14)	0.05	1 (0.07)	0.02
Heart failure	0	n/a	0	n/a	3 (0.21)	0.06
Non-heart-failure cardiovascular	4 (0.27)	0.08	2 (0.14)	0.05	4 (0.28)	0.08

Source: Table A17 above

As mentioned earlier, ascertainment of deaths in this time category was likely incomplete for all treatment groups; patients were routinely followed only to 30 days after cessation of study medication, and later reporting of death was dependent upon non-protocol-specified investigator reporting. For reported deaths in this time category, there were slightly numerically more cardiovascular deaths in the MET group than in the RSG group, with the fewest CV deaths occurring in the SU group. There were no deaths categorized as due to myocardial ischemia in the SU group, while there were 4 and 3 in the RSG and MET groups respectively. The total number of cardiovascular deaths is small, which limits conclusions. The post hoc and unblinded nature of the clinical reviewer's assessment of cause of death is also subject to bias, although every effort at objectivity was made.

For some patients who died more than 30 days after cessation of treatment, from an event that also occurred more than 30 days after cessation of treatment, the clinical reviewer could not find death narratives in the study report. On 28 Jun 07, the clinical reviewer requested that GSK identify the locations of these narratives. On 2 Jul 07, GSK responded:

"Narratives were not provided for these deaths. All of these subjects died more than 30 days after that (sic) last dose of study medication and the event which led to death also occurred more than 30 days after the last dose of study medication. Post-study follow-up for serious adverse events was up to 30 days after the last dose of study medication. The information on the deaths of these subjects was collected on a designated form in the CRF 'Form D'. This form collected the certified case of death, date of death, and whether a post-mortem was performed. Therefore, very limited information is available for these subjects."

After review of all available death narratives, the clinical reviewer did not find evidence of classification of cardiovascular deaths as deaths due to noncardiovascular causes. For each treatment group, there were no narratives for a few deaths which occurred more than 30 days after cessation of treatment and which were due to an event which occurred more than 30 days after cessation of treatment. Overall, the likelihood of significant lack of ascertainment of cardiovascular death seems low. The clinical reviewer did not find evidence of an excess occurrence of cardiovascular death or total mortality among patients treated with rosiglitazone compared to patients treated with glyburide/glibenclamide or metformin.

Cardiovascular Safety

The analyses performed by GSK to assess cardiovascular adverse events are consistent with low and similar rates across treatment groups. The clinical review of cardiovascular safety to date has concentrated both on examining reported rates of events, and on assessing for possible problems with ascertainment and/or categorization of events.

All Serious Cardiovascular Events

The following table presents all serious cardiovascular events identified by the clinical reviewer, by MedDRA System Organ Class and MedDRA preferred term. All terms from the cardiac and vascular System Organ Classes are included. For other System Organ Classes, terms which may represent cardiac or vascular disease are included. The clinical reviewer included all terms which could potentially represent cardiovascular events; some terms are not specific and may represent non-cardiovascular events.

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiac disorders	Any	81 (5.6)	1.6	52 (3.6)	1.2	85 (5.8)	2.0	218 (5.0)	1.5
	Acute coronary syndrome	0	n/a	1 (0.1)	<0.1	3 (0.2)	0.1	4 (0.1)	<0.1
	Acute myocardial infarction	3 (0.2)	0.1	3 (0.2)	0.1	3 (0.2)	0.1	9 (0.2)	0.1
	Angina pectoris	8 (0.5)	0.2	8 (0.6)	0.2	19 (1.3)	0.4	35 (0.8)	0.2
	Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	22 (0.5)	0.2
	Aortic valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arrhythmia	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Arteriosclerosis coronary artery	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Atrial fibrillation	6 (0.4)	0.1	4 (0.3)	0.1	11 (0.8)	0.2	21 (0.5)	0.1
	Atrial flutter	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Atrial tachycardia	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Atrioventricular block complete	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradycardia	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Bundle branch block left	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiac arrest	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac disorder	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiac failure	2 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.3)	0.1	8 (0.2)	0.1
	Cardiac failure acute	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Cardiac failure congestive	4 (0.3)	0.1	1 (0.1)	<0.1	4 (0.3)	0.1	9 (0.2)	0.1
	Cardiac tamponade	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiomyopathy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Congestive cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cor pulmonale	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery disease	12 (0.8)	0.2	6 (0.4)	0.1	16 (1.1)	0.3	34 (0.8)	0.2
	Coronary artery insufficiency	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Coronary artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery stenosis	3 (0.2)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Intracardiac thrombus	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Ischemic cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Left ventricular failure	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Mitral valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Myocardial infarction	20 (1.4)	0.4	8 (0.6)	0.2	15 (1.0)	0.3	43 (1.0)	0.3
	Myocardial ischemia	2 (0.1)	<0.1	4 (0.3)	0.1	2 (0.1)	<0.1	8 (0.2)	0.1
	Pericardial calcification	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Pericarditis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Right ventricular failure	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Silent myocardial infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Sinus arrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Sinus tachycardia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Supraventricular tachycardia	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Tachyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Tachycardia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular dyskinesia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular extrasystoles	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular fibrillation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular tachycardia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
General disorders and administration site conditions	Any (CV or non-CV)	19 (1.3)	0.4	14 (1.0)	0.3	21 (1.4)	0.4	54 (1.2)	0.4
	Chest discomfort	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Chest pain	1 (0.1)	<0.1	0	n/a	3 (0.2)	0.1	4 (0.1)	<0.1
	Edema peripheral	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Generalized edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Local swelling	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
Hepatobiliary disorders	Any (CV or non-CV)	11 (0.8)	0.2	7 (0.5)	0.2	8 (0.6)	0.2	26 (0.6)	0.2
	Ischemic hepatitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Injury, poisoning and procedural complications	Any (CV or non-CV)	41 (2.8)	0.8	39 (2.7)	0.9	40 (2.8)	0.8	120 (2.8)	0.9
	Coronary artery restenosis	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
Nervous system disorders	Any (CV or non-CV)	31 (2.1)	0.6	30 (2.1)	0.7	42 (2.9)	0.9	103 (2.4)	0.7
	Carotid artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Cerebellar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral hemorrhage	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral infarction	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral ischemia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cerebrovascular accident	9 (0.6)	0.2	8 (0.6)	0.2	11 (0.8)	0.2	28 (0.6)	0.2
	Hemorrhagic cerebral infarction	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Intracranial aneurysm	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Subarachnoid hemorrhage	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Syncope	2 (0.1)	<0.1	3 (0.2)	0.1	7 (0.5)	0.1	12 (0.3)	0.1
	Syncope vasovagal	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Transient ischemic attack	3 (0.2)	0.1	3 (0.2)	0.1	5 (0.3)	0.1	11 (0.3)	0.1
Respiratory, thoracic and mediastinal disorders	Any (CV or non-CV)	24 (1.6)	0.5	16 (1.1)	0.4	13 (0.9)	0.3	53 (1.2)	0.4
	Acute pulmonary edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Brain hypoxia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Dyspnea	4 (0.3)	0.1	2 (0.1)	<0.1	0	n/a	6 (0.1)	<0.1
	Pulmonary edema	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Pulmonary embolism	2 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	4 (0.1)	<0.1
Vascular disorders	Any	18 (1.2)	0.4	12 (0.8)	0.3	12 (0.8)	0.2	42 (1.0)	0.3
	Aneurysm ruptured	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic aneurysm	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Aortic stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Arterial occlusive disease	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Arterial stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arterial thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Arteritis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Circulatory collapse	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Deep vein thrombosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Embolism	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Extremity necrosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Femoral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Hematoma	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Hemodynamic instability	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hemorrhage	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hypertension	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Hypertensive crisis	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Hypotension	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Intermittent claudication	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ischemic limb pain	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Labile hypertension	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Peripheral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Varicose vein	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Vascular stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Venous insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Venous thrombosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Visceral arterial ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1

Source: ADOPT study report, Table 8.2.3.1, beg pg 4011

Few individual serious cardiovascular adverse event terms occurred more frequently among RSG group patients than among comparator group patients. Out of the above 104 serious adverse cardiovascular event terms that occurred in any patient, the following 4 individual terms were recorded as SAEs for ≥1% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.1 more for the RSG group than for one of the comparator groups.

Table A20: Individual Cardiovascular SAE Terms that Were Recorded for ≥ 1% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.1 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	22 (0.5)	0.2
Coronary artery disease	12 (0.8)	0.2	6 (0.4)	0.1	16 (1.1)	0.3	34 (0.8)	0.2
Myocardial infarction	20 (1.4)	0.4	8 (0.6)	0.2	15 (1.0)	0.3	43 (1.0)	0.3
Dyspnea	4 (0.3)	0.1	1 (0.1)	<0.1)	0	n/a	6 (0.1)	<0.1

Source: Table A19 above

For the above terms, none were recorded as serious adverse cardiovascular events for ≥2% more RSG group patients than for patients in one of the comparator groups. Only myocardial infarction had a rate/100 PY that was ≥0.2 more for the RSG group than for one of the comparator groups (0.4 RSG, 0.2 SU, 0.3 MET). The single event term of myocardial infaretion would not include all terms which are likely to represent a serious myocardial ischemic event; for example, terms such as acute myocardial infarction and acute coronary syndrome were also used as individual terms in Table A19 above. A more complete picture of myocardial ischemic event rates may be obtained by constructing a group of events which are likely to represent myocardial isehemia. Analyses using groupings for myocardial ischemic events and other categories of cardiovascular adverse events are discussed in later sections.

The table below includes both serious and nonserious eardiovascular events from the study. All terms from the eardiae and vascular System Organ Classes are included. For other System Organ Classes, terms which may represent cardiac or vascular disease are ineluded. The clinical reviewer included all terms which could potentially represent cardiovaseular events; some terms are not specific and may represent non-cardiovascular events.

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiac disorders	Any	191 (13.1)	3.9	157 (10.9)	3.7	220 (15.1)	4.5	568 (13.1)	4.0
	Acute coronary syndrome	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	5 (0.1)	<0.1
	Acute myocardial infarction	3 (0.2)	0.1	3 (0.2)	0.1	3 (0.2)	0.1	9 (0.2)	0.1
	Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
	Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	8 (0.6)	0.2	23 (0.5)	0.2
	Aortic valve disease	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (<0.1)	<0.1
	Aortic valve disease mixed	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve incompetence	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic valve sclerosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arrhythmia	2 (0.1)	<0.1	14 (1.0)	0.3	6 (0.4)	0.1	22 (0.5)	0.2
	Arrhythmia supraventricular	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis coronary artery	0	n/a	3 (0.2)	0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Atrial fibrillation	26 (1.8)	0.5	17 (1.2)	0.4	26 (1.8)	0.5	69 (1.6)	0.5
	Atrial flutter	2 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.3)	0.1	8 (0.2)	0.1
	Atrial hypertrophy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Atrial tachycardia	1 (0.1)	<0.1	3 (0.2)	0.1	0	n/a	4 (0.1)	<0.1
	Atrial thrombosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Atrioventricular block	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Atrioventricular block complete	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Atrioventricular block first degree	12 (0.8)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	26 (0.6)	0.2

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Atrioventricular block second degree	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Bradyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradycardia	7 (0.5)	0.1	5 (0.3)	0.1	6 (0.4)	0.1	18 (0.4)	0.1
	Bundle branch block	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bundle branch block bilateral	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Bundle branch block left	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.3)	0.1	9 (0.2)	0.1
	Bundle branch block right	2 (0.1)	<0.1	3 (0.2)	0.1	8 (0.6)	0.2	13 (0.3)	0.1
	Cardiac aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cardiac arrest	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac disorder	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cardiac failure	6 (0.4)	0.1	3 (0.2)	0.1	5 (0.3)	0.1	14 (0.3)	0.1
	Cardiac failure acute	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Cardiac failure congestive	8 (0.5)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	18 (0.4)	0.1
	Cardiac flutter	2 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac tamponade	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiac valve disease	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiomegaly	6 (0.4)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	10 (0.2)	0.1
	Cardiomyopathy	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.3)	0.1	6 (0.1)	<0.1
	Cardiovascular deconditioning	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiovascular disorder	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Congestive cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cor pulmonale	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery disease	26 (1.8)	0.5	17 (1.2)	0.4	31 (2.1)	0.6	74 (1.7)	0.5
	Coronary artery insufficiency	0	n/a	3 (0.2)	0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Coronary artery occlusion	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Coronary artery stenosis	3 (0.2)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Cyanosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Diastolic dysfunction	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Dilatation atrial	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Dilatation ventricular	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Extrasystoles	4 (0.3)	0.1	1 (0.1)	<0.1	3 (0.2)	0.1	8 (0.2)	0.1
	Heart valve insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hypertensive heart disease	0	n/a	2 (0.1)	<0.1	5 (0.3)	0.1	7 (0.2)	<0.1
	Intracardiac thrombus	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Ischemic cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Left ventricular failure	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Mitral valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Mitral valve incompetence	6 (0.4)	0.1	2 (0.1)	<0.1	5 (0.3)	0.1	13 (0.3)	0.1
	Mitral valve prolapse	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Myocardial infarction	22 (1.5)	0.4	11 (0.8)	0.3	18 (1.2)	0.4	51 (1.2)	0.4
	Myocardial ischemia	7 (0.5)	0.1	6 (0.4)	0.1	8 (0.6)	0.2	21 (0.5)	0.1
	Palpitations	24 (1.6)	0.5	20 (1.4)	0.5	36 (2.5)	0.7	80 (1.8)	0.6
	Pericardial calcification	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pericardial effusion	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pericarditis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Postinfarction angina	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Pulmonary valve incompetence	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Right ventricular failure	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Sick sinus syndrome	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Silent myocardial infarction	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Sinus arrhythmia	0	n/a	0	n/a	3 (0.2)	0.1	3 (0.1)	<0.1
	Sinus bradycardia	6 (0.4)	0.1	2 (0.1)	<0.1	6 (0.4)	0.1	14 (0.3)	0.1
	Sinus tachycardia	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Supraventricular extrasystoles	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Supraventricular tachycardia	2 (0.1)	<0.1	6 (0.4)	0.1	3 (0.2)	0.1	11 (0.3)	0.1
	Tachyarrhythmia	2 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Tachycardia	8 (0.5)	0.2	10 (0.7)	0.2	7 (0.5)	0.1	25 (0.6)	0.2
	Tachycardia paroxysmal	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Tricuspid valve incompetence	3 (0.2)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Ventricular arrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ventricular dysfunction	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	5 (0.1)	<0.1
	Ventricular dyskinesia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular extrasystoles	6 (0.4)	0.1	5 (0.3)	0.1	3 (0.2)	0.1	14 (0.3)	<0.1
	Ventricular fibrillation	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Ventricular hypertrophy	5 (0.3)	0.1	6 (0.4)	0.1	5 (0.3)	0.1	16 (0.4)	<0.1
	Ventricular hypokinesia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ventricular tachycardia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Eye disorders	Any (CV or non-CV)	250 (17.2)	5.0	207 (14.4)	4.9	222 (15.3)	4.5	679 (15.6)	4.8
	Macular ischemia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ocular vascular disorder	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Optic ischemic neuropathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
General disorders and administration site conditions	Any (CV or non-CV)	505 (34.7)	10.2	423 (29.4)	10.0	432 (29.7)	8.8	1360 (31.3)	9.6
	Chest discomfort	7 (0.5)	0.1	4 (0.3)	0.1	5 (0.3)	0.1	16 (0.4)	0.1
	Chest pain	12 (0.8)	0.2	7 (0.5)	0.2	14 (1.0)	0.3	33 (0.8)	0.2
	Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
	Edema face	2 (0.1)	<0.1	0	n/a	4 (0.3)	0.1	6 (0.1)	<0.1
	Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
	Edema gravitational	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Edema mucosal	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
	Edema pitting	4 (0.3)	0.1	5 (0.3)	0.1	0	n/a	9 (0.2)	0.1
	Local swelling	4 (0.3)	0.1	6 (0.4)	0.1	7 (0.5)	0.1	17 (0.4)	0.1
Hepatobiliary disorders	Any (CV or non-CV)	36 (2.5)	0.7	33 (2.3)	0.8	42 (2.9)	0.9	111 (2.6)	0.8
	Ischemic hepatitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
Injury, poisoning and procedural complications	Any (CV or non-CV)	462 (31.7)	9.3	384 (26.6)	9.0	453 (31.2)	9.2	1299 (29.9)	9.2
	Cardiac procedure complication	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery restenosis	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Stent occlusion	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
Investigations	Any (CV or non-CV)	321 (22.0)	6.5	254 (17.6)	6.0	267 (18.4)	5.4	842 (19.4)	6.0
	Abdominal bruit	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Blood pressure decreased	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Blood pressure diastolic decreased	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Blood pressure increased	12 (0.8)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	22 (0.5)	0.2
	Blood pressure systolic increased	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiac murmur	15 (1.0)	0.3	9 (0.6)	0.2	14 (1.0)	0.3	38 (0.9)	0.3
	Cardiac murmur functional	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid bruit	5 (0.3)	0.1	3 (0.2)	0.1	6 (0.4)	0.1	14 (0.3)	0.1
	Catheterization cardiac abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	ECG signs of myocardial ischemia	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	ECG signs of ventricular hypertrophy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Ejection fraction abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ejection fraction decreased	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Electrocardiogram PQ interval prolonged	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram PR shortened	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram Q wave abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram Q waves	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram QRS complex abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram QT prolonged	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram ST segment abnormal	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Electrocardiogram ST segment depression	0	n/a	1 (0.1)	<0.1	3 (0.2)	0.1	4 (0.1)	<0.1
	Electrocardiogram ST-T change	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram ST-T abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram T wave abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram T wave amplitude decreased	2 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Electrocardiogram T wave inversion	0	n/a	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Electrocardiogram abnormal	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Electrocardiogram change	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Electrocardiogram repolarization abnormality	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Femoral bruit	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Gallop rhythm present	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Heart rate decreased	2 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	3 (0.1)	<0.1
	Heart rate increased	7 (0.5)	0.1	3 (0.2)	0.1	4 (0.3)	0.1	14 (0.3)	0.1
	Heart rate irregular	3 (0.2)	0.1	9 (0.6)	0.2	5 (0.3)	0.1	17 (0.4)	0.1
	Pulse absent	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Pulse pressure decreased	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
Nervous system disorders	Any (CV or non-CV)	548 (37.6)	11.1	513 (35.6)	12.1	554 (38.1)	11.3	1615 (37.1)	11.5
	Aphasia	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Carotid artery atheroma	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Carotid artery disease	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Carotid artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid artery stenosis	3 (0.2)	0.1	7 (0.5)	0.2	6 (0.4)	0.1	16 (0.4)	0.1
	Cerebellar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral arteriosclerosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral hemorrhage	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral infarction	0	n/a	0	n/a	3 (0.2)	0.1	3 (0.1)	<0.1
	Cerebral ischemia	0	n/a	4 (0.3)	0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Cerebrovascular accident	12 (0.8)	0.2	9 (0.6)	0.2	12 (0.8)	0.2	33 (0.8)	0.2
	Cerebrovascular disorder	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebrovascular insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hemorrhagic cerebral infarction	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Intracranial aneurysm	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Lacunar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Subarachnoid hemorrhage	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
	Syncope vasovagal	6 (0.4)	0.1	4 (0.3)	0.1	6 (0.4)	0.1	16 (0.4)	0.1
	Transient ischemic attack	7 (0.5)	0.1	6 (0.4)	0.1	11 (0.8)	0.2	24 (0.6)	0.2
Respiratory, thoracic and mediastinal disorders	Any (CV or non-CV)	421 (28.9)	8.5	368 (25.5)	8.7	310 (21.3)	6.3	910 (20.9)	6.5
	Acute pulmonary edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Brain hypoxia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2.9)	0.9	159 (3.7)	1.1
	Dyspnea at rest	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Dyspnea exacerbated	4 (0.3)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4
	Nocturnal dyspnea	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pulmonary edema	3 (0.2)	0.1	3 (0.2)	0.1	2 (0.1)	<0.1	8 (0.2)	0.1
	Pulmonary embolism	3 (0.2)	0.1	3 (0.2)	0.1	0	n/a	6 (0.1)	<0.1
	Pulmonary hypertension	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
Vascular disorders	Any	328 (22.5)	6.6	327 (22.7)	7.7	391 (26.9)	8.0	1046 (24.0)	7.4
	Aneurysm ruptured	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiodysplasia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiopathy	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Aortic aneurysm	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.4)	0.1	9 (0.2)	0.1
	Aortic arteriosclerosis	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Aortic stenosis	6 (0.4)	0.1	2 (0.1)	<0.1	3 (0.2)	0.1	11 (0.3)	0.1
	Arterial occlusive disease	2 (0.1)	<0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.1)	<0.1
	Arterial rupture	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Arterial stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arterial thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis	2 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.2)	0.1	7 (0.2)	<0.1
	Arteritis	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Artery dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Blood pressure fluctuation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Circulatory collapse	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Deep vein thrombosis	3 (0.2)	0.1	2 (0.1)	<0.1	0	n/a	5 (0.1)	<0.1
	Diabetic microangiopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Embolism	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Essential hypertension	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Extremity necrosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Femoral arterial stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Femoral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Flushing	4 (0.3)	0.1	8 (0.6)	0.2	2 (0.1)	<0.1	14 (0.3)	0.1
	Hematoma	11 (0.8)	0.2	2 (0.1)	<0.1	14 (1.0)	0.3	27 (0.6)	0.2
	Hemodynamic instability	1 (0.1)	<0.1	0	n/a	0	n/a	1 (0.1)	<0.1
	Hemorrhage	3 (0.2)	0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.1)	<0.1
	Hot flush	19 (1.3)	0.4	13 (0.9)	0.3	28 (1.9)	0.6	60 (1.4)	0.4
	Hypertension	216 (14.8)	4.4	253 (17.6)	6.0	297 (20.4)	6.1	766 (17.6)	5.4
	Hypertensive crisis	3 (0.2)	0.1	2 (0.1)	<0.1	4 (0.3)	0.1	9 (0.2)	0.1
	Hypotension	13 (0.9)	0.3	12 (0.2)	0.3	12 (0.8)	0.2	28 (0.6)	0.2
	Iliac artery stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Intermittent claudication	6 (0.4)	0.1	6 (0.4)	0.1	4 (0.3)	0.1	16 (0.4)	0.1
	Ischemic limb pain	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Labile blood pressure	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Labile hypertension	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.4)	0.1	9 (0.2)	0.1
	Lymphedema	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Orthostatic hypertension	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Orthostatic hypotension	2 (0.1)	<0.1	5 (0.3)	0.1	5 (0.3)	0.1	12 (0.3)	0.1
	Pallor	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Peripheral arterial occlusive disease	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Peripheral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral artery dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Peripheral ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral vascular disorder	2 (0.1)	<0.1	5 (0.3)	0.1	3 (0.2)	0.1	10 (0.2)	0.1
	Periphlebitis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Phlebitis	9 (0.6)	0.2	7 (0.5)	0.2	6 (0.4)	0.1	22 (0.5)	0.2
	Phlebitis superficial	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Phlebolith	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Poor peripheral circulation	3 (0.2)	<0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Raynaud's phenomenon	2 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.3)	0.1	8 (0.2)	0.1
	Systolic hypertension	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Temporal arteritis	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Thrombophlebitis	3 (0.2)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Thrombophlebitis superficial	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
	Thrombosis	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Varicose ulceration	0	n/a	3 (0.2)	0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Varicose vein	15 (1.0)	0.3	8 (0.6)	0.2	13 (0.9)	0.3	36 (0.8)	0.3
	Vaseular calcification	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Vascular rupture	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Vascular shunt	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vascular stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasculitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasodilation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasospasm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Vein disorder	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Venous insufficiency	15 (1.0)	0.3	12 (0.8)	0.3	12 (0.8)	0.2	39 (0.9)	0.3
	Venous occlusion	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Venous stasis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Venous thrombosis	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Visceral arterial ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1

Source: ADOPT study report, Table 8.2.1, beg pg 3564

Out of some 240 cardiovascular adverse event Preferred Terms in the above table, few occurred with greater frequency among RSG group patients than among patients in the comparator groups. The following terms were recorded as adverse cardiovascular events for ≥1% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.1 more for the RSG group than for one of the comparator groups.

Table A22: Individual Cardiovascular AE Terms (Combined Serious and Nonserious) that Were Recorded for ≥ 1% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.1 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
Atrial fibrillation	26 (1.8)	0.5	17 (1.2)	0.4	26 (1.8)	0.5	69 (1.6)	0.5
Atrioventricular block first degree	12 (0.8)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	26 (0.6)	0.2
Cardiac failure congestive	8 (0.5)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	18 (0.4)	0.1
Coronary artery disease	26 (1.8)	0.5	17 (1.2)	0.4	31 (2.1)	0.6	74 (1.7)	0.5
Myocardial infarction	22 (1.5)	0.4	11 (0.8)	0.3	18 (1.2)	0.4	51 (1.2)	0.4
Tachycardia	8 (0.5)	0.2	10 (0.7)	0.2	7 (0.5)	0.1	25 (0.6)	0.2
Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
Edema pitting	4 (0.3)	0.1	5 (0.3)	0.1	0	n/a	9 (0.2)	0.1
Blood pressure increased	12 (0.8)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	22 (0.5)	0.2
Cardiac murmur	15 (1.0)	0.3	9 (0.6)	0.2	14 (1.0)	0.3	38 (0.9)	0.3
Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2.9)	0.9	159 (3.7)	1.1
Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4
Angiopathy	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
Deep vein thrombosis	3 (0.2)	0.1	2 (0.1)	<0.1	0	n/a	5 (0.1)	<0.1
Hematoma	11 (0.8)	0.2	2 (0.1)	<0.1	14 (1.0)	0.3	27 (0.6)	0.2
Hypotension	13 (0.9)	0.3	12 (0.2)	0.3	12 (0.8)	0.2	28 (0.6)	0.2
Phlebitis	9 (0.6)	0.2	7 (0.5)	0.2	6 (0.4)	0.1	22 (0.5)	0.2
Thrombophlebitis superficial	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
Varicose vein	15 (1.0)	0.3	8 (0.6)	0.2	13 (0.9)	0.3	36 (0.8)	0.3
Venous insufficiency	15 (1.0)	0.3	12 (0.8)	0.3	12 (0.8)	0.2	39 (0.9)	0.3

Source: Table A21 above

The following terms were recorded as adverse cardiovascular events for ≥2% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.2 more for the RSG group than for one of the comparator groups.

Table A23: Individual Cardiovascular AE Terms (Combined Serious and Nonserious) that Were Recorded for ≥ 2% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.2 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2 9)	0.9	159 (3.7)	1.1
Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4

Source: Table A22 above

Angina pectoris occurred numerically somewhat more frequently among RSG-treated patients than among SU-treated patients. Edema-related events occurred more frequently among RSG-treated patients than among patients in either of the other treatment groups.

At the time this briefing document is being prepared, the clinical reviewer is examining all narratives of adverse events that were included in the ADOPT study report; these narratives cover some 1700 pages. This review is intended to confirm appropriate assignment of event terms, appropriate characterization of adverse event outcomes, and inclusion of seeondary but also serious adverse events which may have occurred in a given patient. To date, no miselassifieation or omissions have been identified.

Cardiovascular Event Grouping Analyses by GSK

The applieant designated groupings of eardiovaseular adverse events of speeial interest. These four groupings inelude myoeardial isehemia; arrhythmia and eonduetion disorders; HF and pulmonary edema; and "other". The MedDRA lower level terms which were included in each of these groupings, and which had at least one patient reporting an event, are ineluded in Appendix 12. Lower level MedDRA terms that GSK selected for the AEs of special interest that were not experienced by at least one patient were not included in the ADOPT study report. The clinical reviewer examined (blinded to treatment assignment) all terms which were assigned to eaeh of the CV event groupings, to assess for appropriateness of eategorization and ascertainment. In general, assignment of terms to eaeh group appeared appropriate. However, there were some terms which were included in the "other CV events" category which could reasonably have been assigned to one of the other categories. Most terms in the "other CV events" category werc relatcd to valvular disease, pericardial disease and nonspecific ECG findings. The following table lists thc terms from the "other CV events" category which the clinical reviewer identified as terms which could reasonably have been assigned to one of the other CV event groupings.

Table A24: MedDRA Lower Level Terms Which Were Assigned to Applicant's Grouping of "Other Cardiovascular Events" Which Might Reasonably Have Been Assigned to Another CV Event Grouping

Lower Level Term Assigned to "Other CV Events" Grouping	CV Event Grouping to Which Term Might Reasonably Have Been Assigned	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiomegaly	HF/ pulm edema	4 (0.28)	0.08	1 (0.07)	0.02	1 (0.07)	0.02	6 (0.14)	0.04
Cardiomyopathy	HF/ pulm edema	1 (0.07)	0.02	1 (0.07)	0.02	4 (0.28)	0.08	6 (0.14)	0.04
Dilatation ventricular	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01
Dilated cardiomyopathy	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01
Electrocardiogram Q wave abnormal	Myocardial ischemia	0	n/a	0	n/a	1 (0.07)	0.02	1 (0.02)	0.01
Heart enlarged	HF/ pulm edema	2 (0.14)	0.04	1 (0.07)	0.02)	1 (0.07)	0.02	4 (0.09)	0.03
Left ventricular dilatation	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01

Source: ADOPT study report Table 8.2.4.3, beg pg 4177

Some of the above terms are somewhat nonspecific, which may account for their assignment to the "other" category. These terms were discussed with Dr. Ellis Unger, FDA cardiologist and Acting Deputy Director of the Office of Surveillance and Epidemiology; he stated that he would not have assigned these terms to the heart failure or myocardial ischemia groupings of CV AEs due to the nonspecificity of the terms. Most of the terms in question are potentially related to heart failure. Even if the HF terms were added to the HF group, their proportions are such that they would not change the overall conclusion regarding relative risk of heart failure (see Table A29 and Figures A12-13 below).

The clinical reviewer is also examining all MedDRA Lower Level Terms which were actually used for events that occurred in ADOPT, to verify that the sets of terms identified by GSK for inclusion in event groupings were fully inclusive. This process is complicated by the fact that Lower Level Terms were included in the groupings, while MedDRA Preferred Terms were used for summary reporting. Cross-checking of thousands of text terms using datasets, and the MedDRA terms dictionary, is required. To date, very few terms have been noted which might reasonably have been added, but a complete cross-check is needed to fully evaluate for ascertainment issues related to selection of terms for CV event groupings.

The following table by GSK summarizes the numbers of events which occurred in each of their specified cardiovascular event groupings.

Table A25: Summary of Numbers of Events Within GSK's Groupings of Cardiovascular Adverse Events: All On-Therapy CV AEs, All On-Therapy CV SAEs, and All CV AEs that Led to Withdrawal (Population of All Patients who Received at Least One Dose of Study Medication)

Preferred Term / Sub-categories	Number of Subjects, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-Therapy AEs	201 (13.8)	4.1	170 (11.8)	4.0	237 (16.3)	4.8
Myocardial ischemia	106 (7.3)	2.1	82 (5.7)	1.9	111 (7.6)	2.3
Angina	64 (4.4)	1.3	45 (3.1)	1.1	69 (4.7)	1.4
Coronary artery disease	39 (2.7)	0.8	33 (2.3)	0.8	48 (3.3)	1.0
Myocardial infarction	27 (1.9)	0.6	18 (1.3)	0.4	23 (1.6)	0.5
Arrhythmia/Conduction	79 (5.4)	1.6	71 (4.9)	1.7	85 (5.8)	1.7
CHF/Pulmonary edema	22 (1.5)	0.4	9 (0.6)	0.2	19 (1.3)	0.4
Other	63 (4.3)	1.3	46 (3.2)	1.1	73 (5.0)	1.5
Subjects with On-therapy SAEs	82 (5.6)	1.7	54 (3.7)	1.3	86 (5.9)	1.8
Myocardial ischemia	55 (3.8)	1.1	43 (3.0)	1.0	60 (4.1)	1.2
Angina	16 (1.1)	0.3	15 (1.0)	0.4	26 (1.8)	0.5
Coronary artery disease	18 (1.2)	0.4	17 (1.2)	0.4	21 (1.4)	0.4
Myocardial infarction	24 (1.6)	0.5	14 (1.0)	0.3	20 (1.4)	0.4
Arrhythmia/Conduction	14 (1.0)	0.3	9 (0.6)	0.2	19 (1.3)	0.4
CHF/Pulmonary edema	12 (0.8)	0.2	3 (0.2)	0.1	12 (0.8)	0.2
Other	7 (0.5)	0.1	4 (0.3)	0.1	1 (0.1)	<0.1
Subjects with On-therapy AEs leading to Withdrawal	26 (1.8)	-	13 (0.9)	-	18 (1.2)	-
Myocardial ischemia	13 (0.9)	-	9 (0.6)	-	12 (0.8)	-
Angina	3 (0.2)	-	3 (0.2)	-	2 (0.1)	-
Coronary artery disease	2 (0.1)	-	2 (0.1)	-	4 (0.3)	-
Myocardial infarction	8 (0.5)	-	6 (0.4)	-	6 (0.4)	-
Arrhythmia/Conduction	1 (0.1)	-	4 (0.3)	-	2 (0.1)	-
CHF/Pulmonary edema	10 (0.7)	-	4 (0.3)	-	5 (0.3)	-
Other	4 (0.3)	-	0	-	0	-

a. Note: Sorted by frequency of adverse events in RSG group.
Data Source: Table 8.2.4.3. Table 8.2.3.3. Table 8.5.1. and *Ad hoc* Table 1707

Source: ADOPT study report, Table 63, pg 174

The percentage of patients with any on-therapy CV event within one of GSK's groupings was numerically highest for the metformin group, followed by the rosiglitazone group and then the sulfonylurea group. Because of lower exposure for sulfonylurea patients, consideration of duration of exposure and therefore the rate of events (e.g. per hundred patient-years) is important. When this is considered, the rate for metformin group patients is numerically somewhat higher than the rate for the other comparators, with an approximately equal rate for the rosiglitazone and sulfonylurea groups. For myocardial ischemia events, the percentage of patients who experienced an event was approximately equal for the rosiglitazone and metformin groups, and somewhat numerically lower for the sulfonylurea group; however, rates/PY were similar for the three groups. Angina events appear to have contributed to the numerical difference in the percentage of patients experiencing a myocardial ischemic event. The percentages of patients with a reported myocardial infarction were 1.9, 1.6 and 1.3% for the rosiglitazone, metformin and sulfonylurea groups, respectively. The myocardial infarction rates/100 PY for these groups were similar at 0.6, 0.5 and 0.4, respectively. For arrhythmia and conduction system events, rates/100 PY were similar for each of the treatment groups. Heart failure and pulmonary edema events occurred at similar rates among

rosiglitazone and metformin group patients, with a slightly numerically lower rate among SU group patients.

For serious on-therapy CV events, the percentage of patients who experienced an event was similar for the rosiglitazone and metformin groups, and slightly numerically lower for the sulfonylurea group. As with overall CV AEs, the percentage of patients for whom a myocardial ischemic event was reported was numerically slightly lower for SU group patients than for RSG or MET group patients, but rates/ 100 PY were similar. The percentages of patients who had a reported SAE of MI were 1.6, 1.4 and 1.0 for the rosiglitazone, metformin and sulfonylurea groups, respectively; rates/ 100 PY for these groups were 0.5, 0.4 and 0.3 respectively. Rates/ 100 PY of serious arrhythmia or conduction system events were similar among treatment groups. The number of reported events of serious heart failure or pulmonary edema was low; a numerically smaller percentage of patients in the SU group had a reported event than did patients in the RSG or MET groups. Rates/ 100 PY of serious heart failure or pulmonary edema were similar among treatment groups.

A slightly higher percentage of patients in the RSG group withdrew from study due to an on-therapy CV AE than did patients in the MET or SU groups. Withdrawal due to heart failure or pulmonary edema contributed to this difference, with 0.7% of RSG group patients withdrawing compared to 0.3% of patients in each of the other groups. A total of 0.5% of RSG group patients withdrew due to MI, while 0.4% of patients in each of the other groups did so.

The effect of the study withdrawal rate on interpretation of adverse event data presents a challenge. Time-to-event analyses take into account censoring of data by subject withdrawal over time. The following tables and Kaplan-Meier curves present time-to-event data for overall CV events and for the CV event groupings.

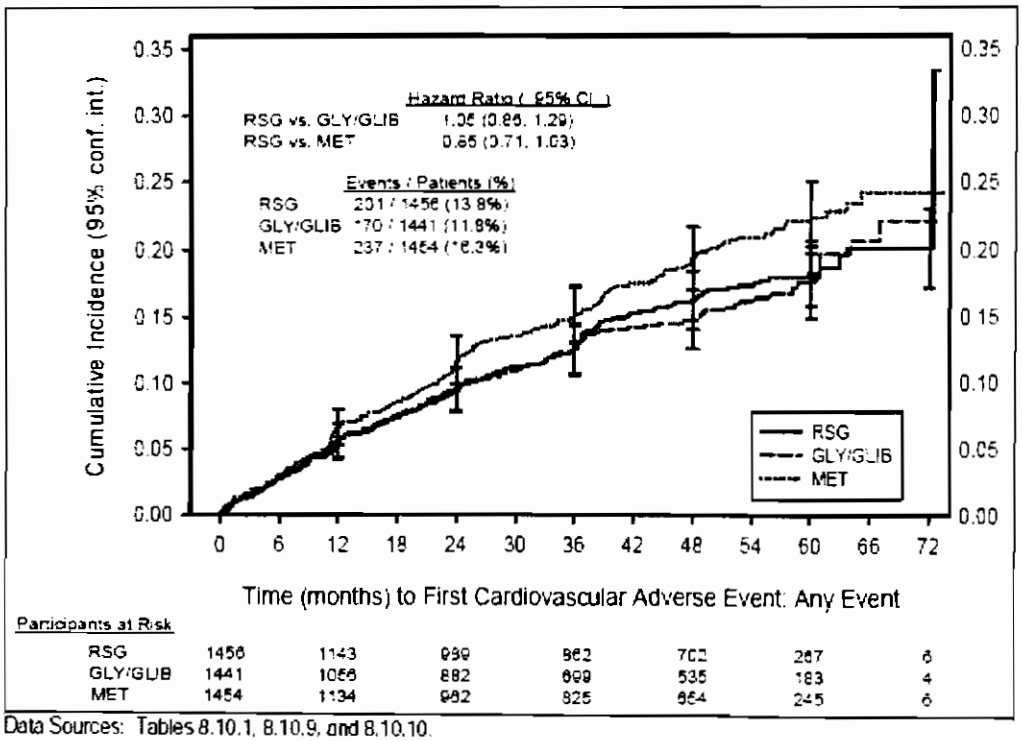
Table A26: Analyses by GSK of Time-to-First Cardiovascular AE and Time-to-First Cardiovascular SAE, Population of All Patients who Received at Least One Dose of Study Medication

All cardiovascular AEs	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with events during study, n	201	170	237
60-month Cumulative Incidence (95% CI)	0.18 (0.16, 0.21)	0.18 (0.15, 0.20)	0.22 (0.20, 0.25)
RSG vs. Control			
Hazard ratio (95% CI)		1.051 (0.857, 1.289)	0.851 (0.705, 1.028)
p-value		0.6338	0.0935
Serious Adverse Events			
Total subjects with events during study, n	82	54	86
60-month Cumulative Incidence (95% CI)	0.08 (0.06, 0.10)	0.06 (0.04, 0.07)	0.08 (0.06, 0.10)
RSG vs. Control			
Hazard ratio (95% CI)		1.378 (0.977, 1.944)	0.990 (0.731, 1.340)
p-value		0.0679	0.9485

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 65, pg 175

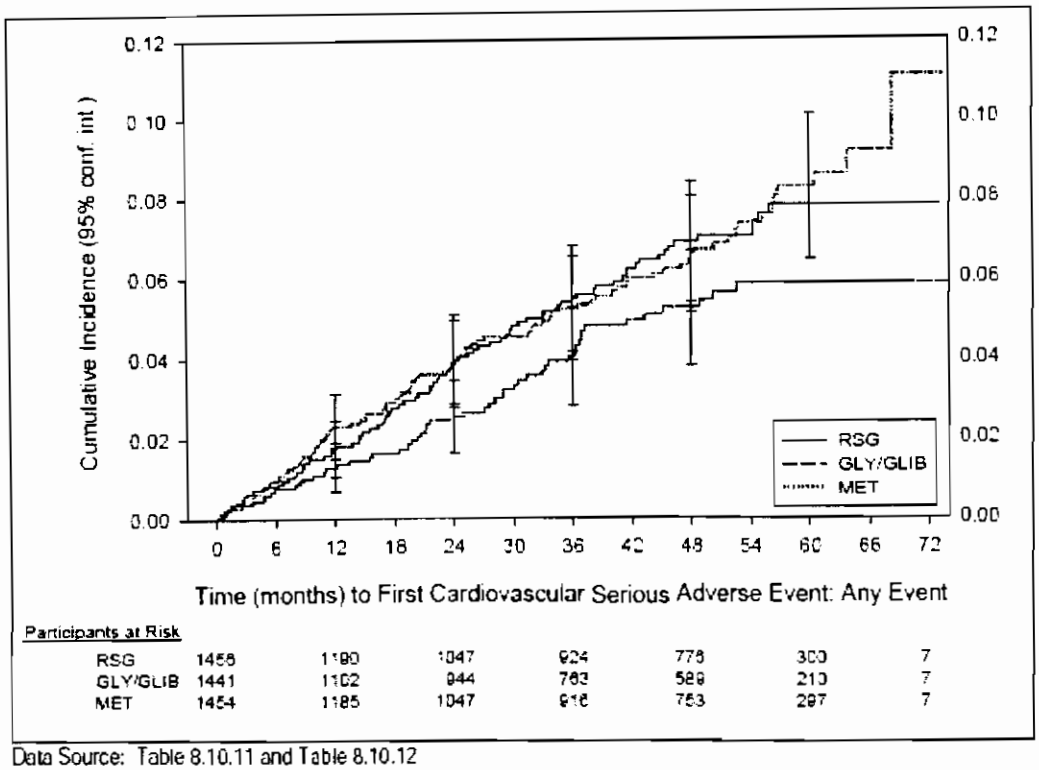
Figure A6: Cumulative Incidence of First Cardiovascular AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Sources: Tables 8.10.1, 8.10.9, and 8.10.10.

Source: ADOPT study report, Figure 44, pg 176

Figure A7: Cumulative Incidence of First Cardiovascular Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 45, pg 177

When considering time-to-event analyses for all CV AEs, or all CV SAEs, 95% confidence intervals for the hazard ratios include 1, and p-values exceed 0.05, for all comparisons of RSG to SU or to MET. If one uses a threshold of a p-value of 0.1, CV events of any severity occurred somewhat less frequently with RSG than with MET, and serious CV SAEs occurred somewhat more frequently with RSG than with SU.

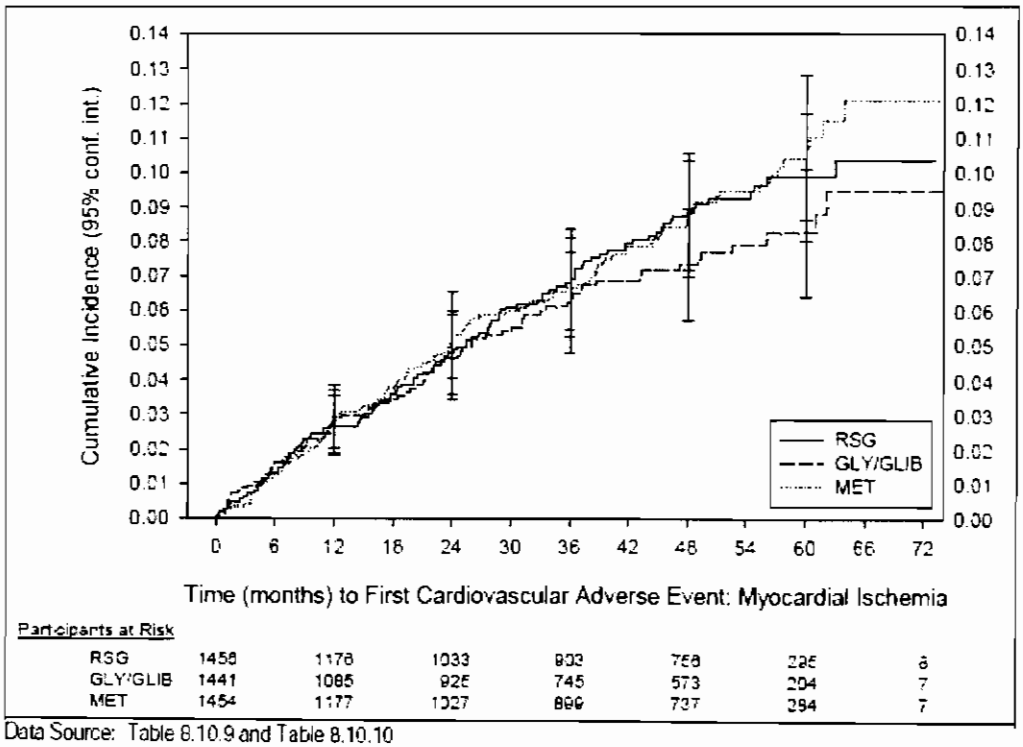
Table A27: Analyses by GSK of Time-to-First Myocardial Ischemia AE and Time-to-First Myocardial Ischemia SAE, Population of All Patients who Received at Least One Dose of Study Medication

Myocardial Ischemia	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with event during study, n	106	82	111
60-month Cumulative Incidence (95% CI)	0.10 (0.08, 0.12)	0.08 (0.06, 0.10)	0.11 (0.09, 0.13)
RSG vs. Control			
Hazard ratio (95% CI)		1.178 (0.882, 1.572)	0.993 (0.760, 1.296)
p-value		0.2667	0.9559
Serious Adverse Events			
Total subjects with event during study, n	55	43	60
60-month Cumulative Incidence (95% CI)	0.05 (0.04, 0.07)	0.05 (0.03, 0.06)	0.06 (0.04, 0.07)
RSG vs. Control			
Hazard ratio (95% CI)		1.161 (0.778, 1.731)	0.955 (0.662, 1.377)
p-value		0.4646	0.8042

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 67, pg 178

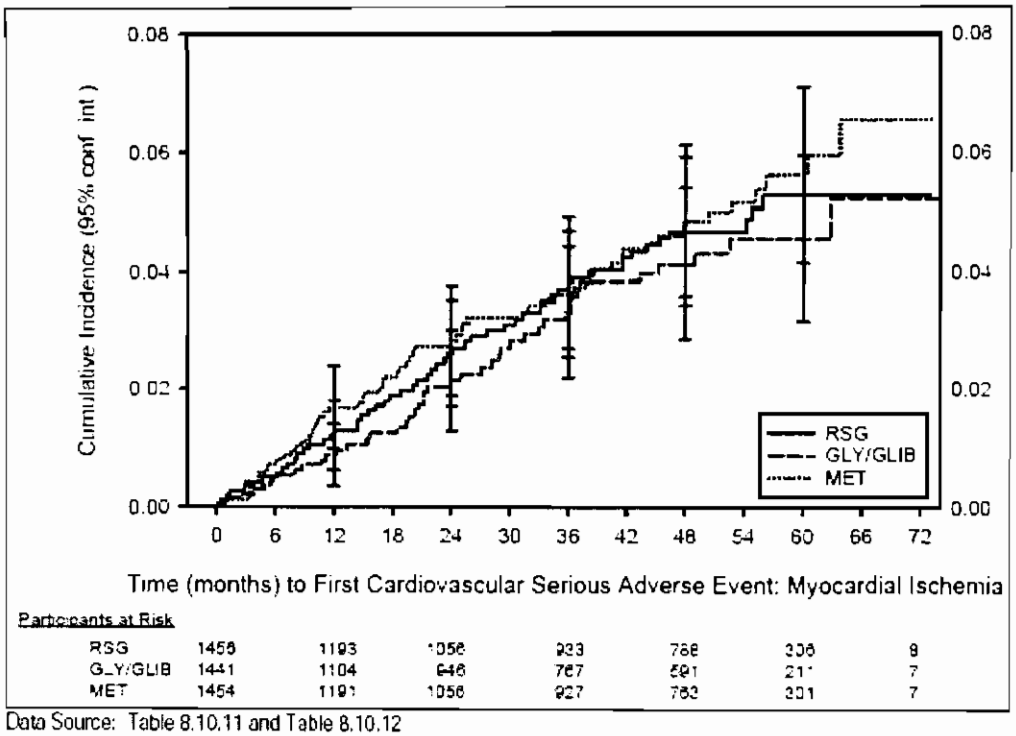
Figure A8: Cumulative Incidence of First Myocardial Ischemia AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 46, pg 179

Figure A9: Cumulative Incidence of First Myocardial Ischemia Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 47, pg 180

When considering time-to-event analyses for myocardial ischemia AEs, or myocardial ischemia SAEs, 95% confidence intervals for the hazard ratios include 1, and all p-values exceed 0.2, for all comparisons of RSG to SU or to MET.

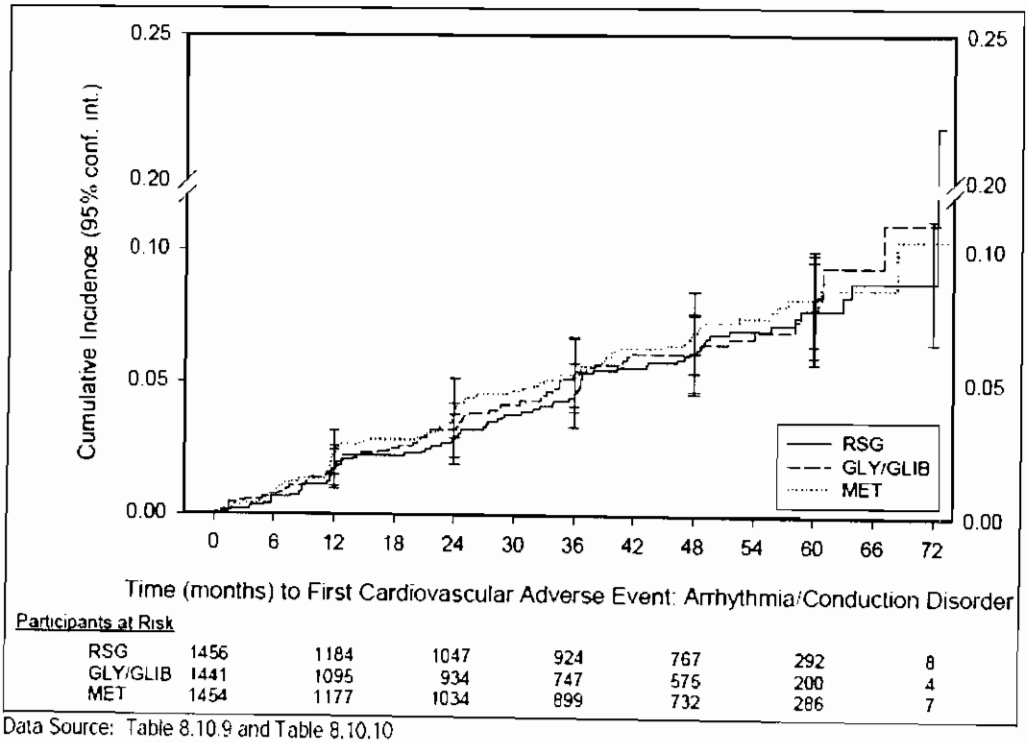
Table A28 Analyses by GSK of Time-to-First Arrhythmia or Conduction Disorder AE and Time-to-First Arrhythmia or Conduction Disorder SAE, Population of All Patients who Received at Least One Dose of Study Medication

Arrhythmia and Conduction Disorders	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with event during study, n	79	71	85
60-month Cumulative Incidence (95% CI)	0.08 (0.06, 0.10)	0.08 (0.06, 0.10)	0.08 (0.06, 0.10)
RSG vs. Control			
Hazard ratio (95% CI)		0.963 (0.699, 1.328)	0.928 (0.683, 1.260)
p-value		0.8204	0.6306
Serious Adverse Events			
Total subjects with event during study, n	14	9	19
60-month Cumulative Incidence (95% CI)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.02 (0.01 0.03)
RSG vs. Control			
Hazard ratio (95% CI)		1.381 (0.597, 3.195)	0.740 (0.371, 1.477)
p-value		0.4510	0.3932

Data Sources: Table 8.10.1 Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report Table 69, pg 181

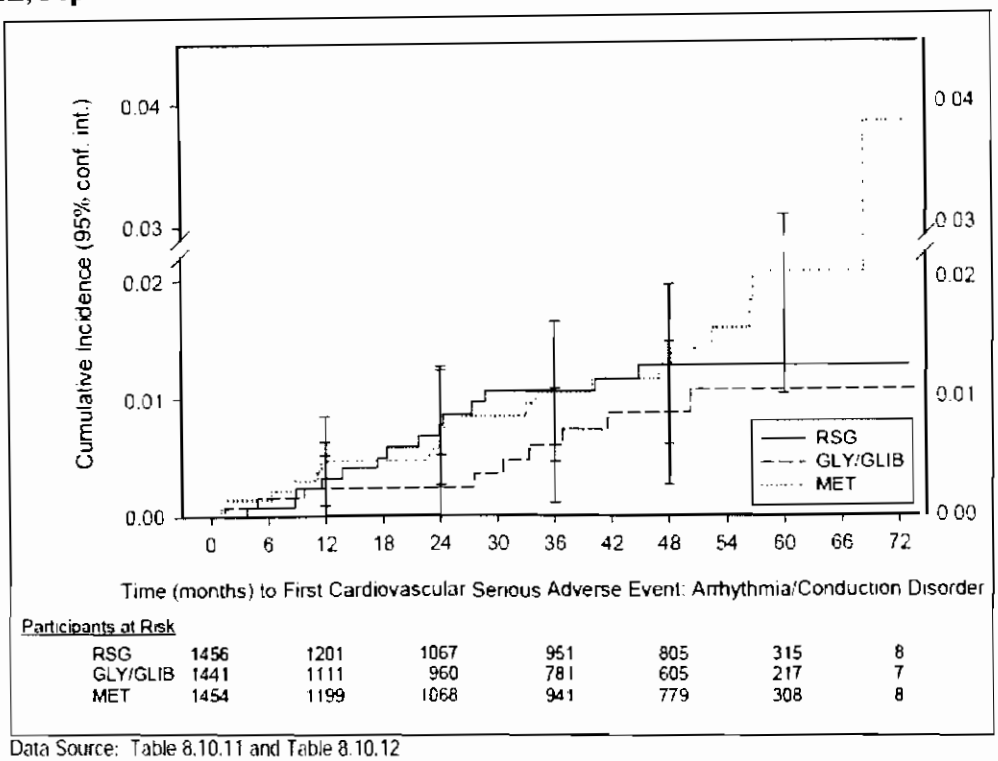
Figure A10: Cumulative Incidence of First Arrhythmia or Conduction Disorder AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 48, pg 182

Figure A11: Cumulative Incidence of First Serious Arrhythmia or Conduction Disorder Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 49, pg 183

When considering time-to-event analyses for arrhythmia or conduction disorder AEs, or arrhythmia or conduction disorder SAEs, 95% confidence intervals for the hazard ratios include 1, and all p-values exceed 0.3, for all comparisons of RSG to SU or to MET.

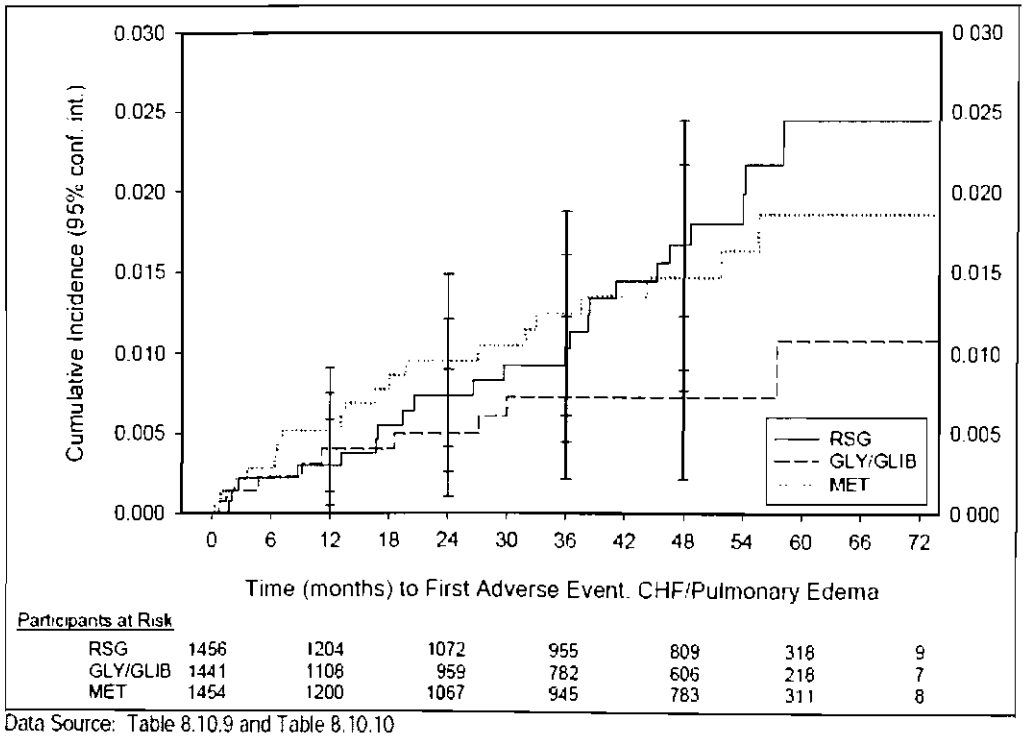
Table A29: Analyses by GSK of Time-to-First Heart Failure or Pulmonary Edema AE and Time-to-First Heart Failure or Pulmonary Edema SAE, Population of All Patients who Received at Least One Dose of Study Medication

CHF/Pulmonary Edema Events	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Number of subjects with events	22	9	19
60-month Cumulative Incidence (95% CI)	0.02 (0.01, 0.04)	0.01 (0.00, 0.02)	0.02 (0.01, 0.03)
RSG vs. Control			
Hazard ratio (95% CI)		2.202 (1.012, 4.789)	1.222 (0.661, 2.259)
p-value		0.0465	0.5231
Serious Adverse Events			
Number of subjects with events, n	12	3	12
60-month Cumulative Incidence (95% CI)	0.01 (0.01, 0.02)	0.00 (0.00, 0.01)	0.01 (0.01, 0.02)
RSG vs. Control			
Hazard ratio (95% CI)		3.618 (1.019, 12.840)	1.068 (0.479, 2.379)
p-value		0.0466	0.8727

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

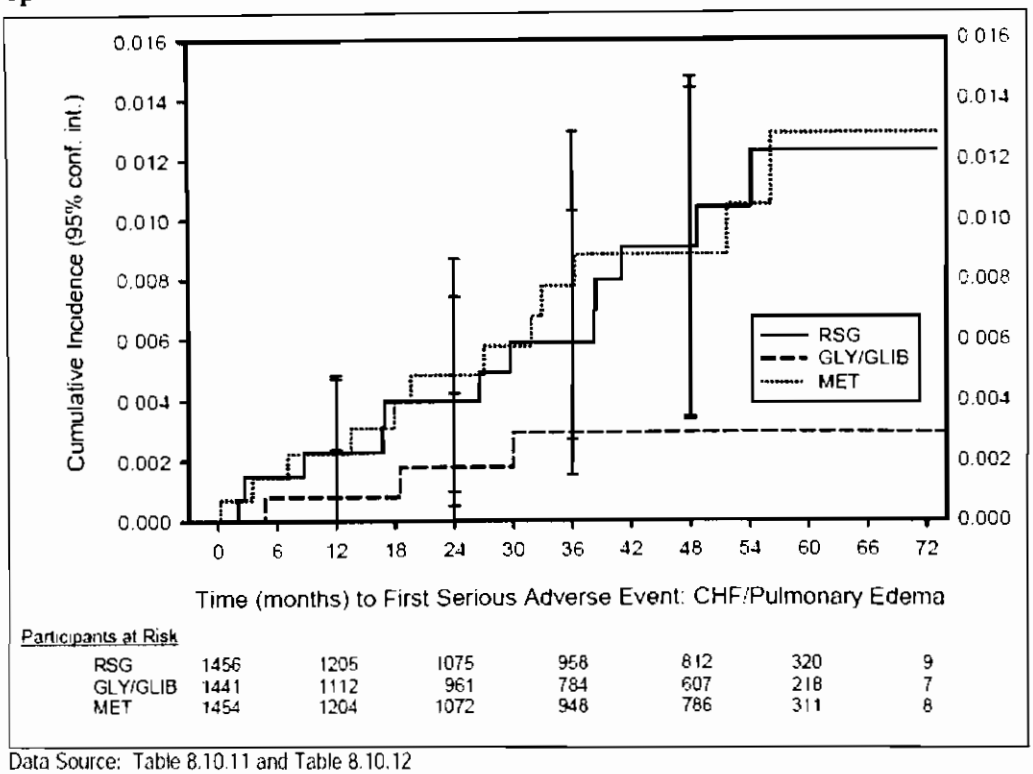
Source: ADOPT study report, Table 71, pg 184

Figure A12: Cumulative Incidence of First Heart Failure or Pulmonary Edema AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Source: ADOPT study report, Figure 50, pg 185

Figure A13: Cumulative Incidence of First Serious Heart Failure or Pulmonary Edema AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 51, pg 186

When considering time-to-event analyses for heart failure or pulmonary edema AEs, or for heart failure or pulmonary edema SAEs, the rate of heart failure for the RSG group exceeded that of the SU group, for both overall HF/pulm edema AEs (HR 2.2, 95% CI 1.01, 4.79) and serious HF/pulm edema AEs (HR 3.6, 95% CI 1.02, 12.84). For the comparison of RSG to MET, 95% CIs included 1, and p-values for both overall and serious AEs exceeded 0.5.

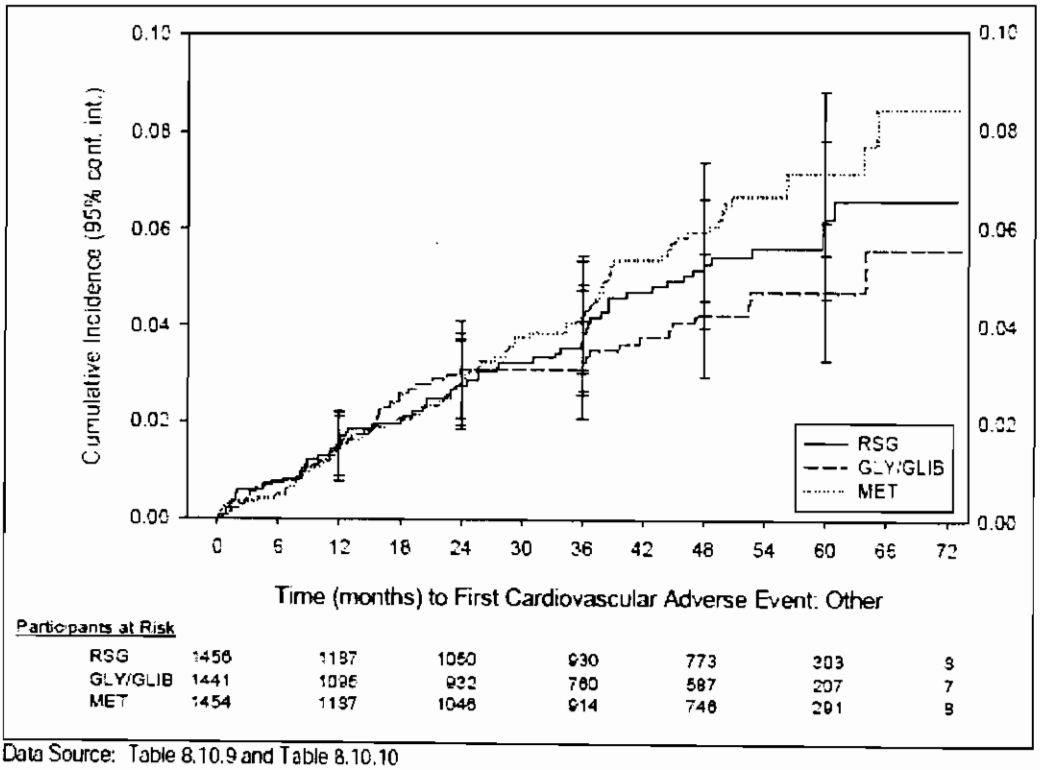
Table A30: Analyses by GSK of Time-to-First Cardiovascular Event Categorized as "Other" and First Serious Cardiovascular Event Categorized as "Other", Population of All Patients Who Received at Least One Dose of Study Medication

Cardiovascular Events Categorized as "Other"	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Subjects with events during study, n	63	46	73
60-month Cumulative Incidence (95% CI)	0.06 (0.05, 0.08)	0.05 (0.03, 0.06)	0.07 (0.05, 0.09)
RSG vs. Control			
Hazard ratio (95% CI)		1.195 (0.816, 1.748)	0.859 (0.613, 1.203)
p-value		0.3597	0.3762
Serious Adverse Events			
Subjects with events during study, n	7	4	1
60-month Cumulative Incidence (95% CI)	0.01 (0, 0.01)	0.01 (0, 0.01)	0 (0, 0.01)
RSG vs. Control			
Hazard ratio (95% CI)		1.561 (0.455, 5.353)	7.410 (0.911, 60.278)
p-value		0.4791	0.0611

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 76, pg 192

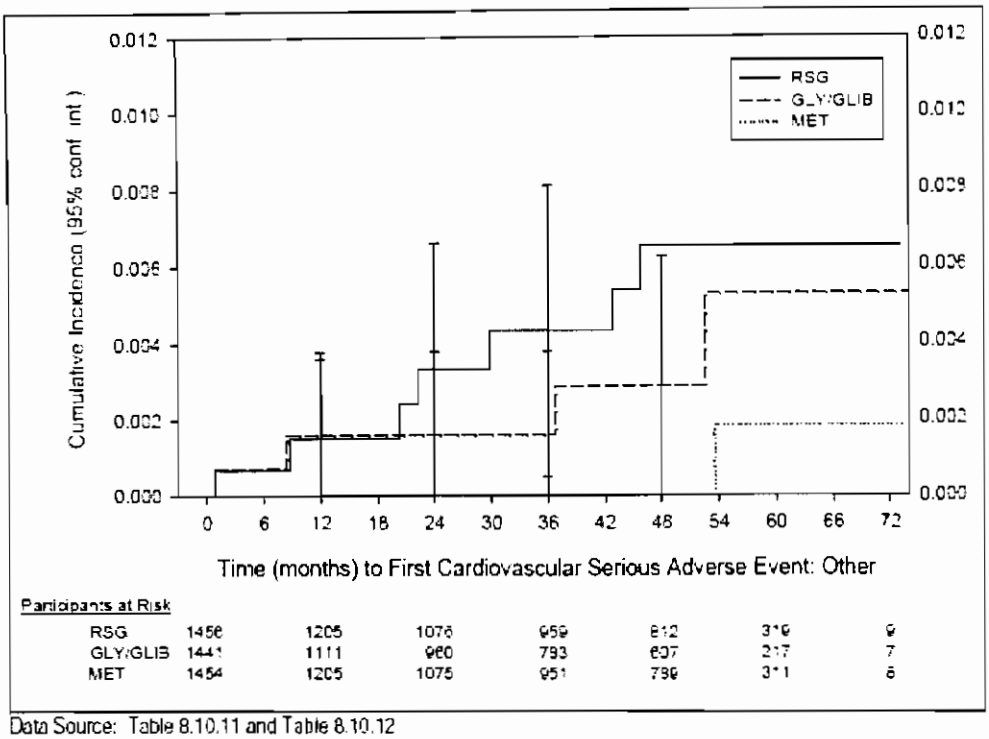
Figure A14: Cumulative Incidence of First Cardiovascular AE Classified as "Other" (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 53, pg 193

Figure A15: Cumulative Incidence of First Serious Cardiovascular AE Classified as "Other", Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 54, pg 194

When considering time-to-event analyses for all CV AEs and SAEs classified as "other", 95% confidence intervals for the hazard ratios include 1, and p-values exceed 0.05, for all comparisons of RSG to SU or to MET. The rate of serious AEs within this category was low; there were 7, 4 and 1 events, respectively, in the RSG, SU and MET groups. For the eomparison of RSG to MET, the HR was 7.4, with a very wide confidenee interval of 0.91 to 60.28 due to the low event rate, and a p-value of 0.06.

Time-to-Event Analyses of Serious Cardiovascular Endpoints by FDA Statistical Reviewer

Ms. Joy Mele performed time-to-event analyses for multiple eardiovascular endpoints. Time-to-event analyses are useful when withdrawal rates differ between treatment groups. In these analyses, patients who discontinue for any reason are censored and dropped from the group at risk at that point in time; therefore the probability of not having an event at any given time is computed based on the number of patients in the risk group at that time. This adjustment to the number at risk as patients drop out allows one to obtain an overall risk, accounting for changes in the risk set. This is particularly important for this trial, in which dropout rates differ between treatment groups.

Please refer to Ms. Mele's briefing document for further explanation of her methods. Her proportional hazards model differed slightly from that of GSK. In addition to terms for treatment and number of major cardiovascular risk factors, she also included gender as a stratifier sinee randomization had been stratified on gender. The following table presents the results of Ms. Mele's analyses.

Table A31: Proportional Hazards Model Analysis Results for Ischemic et al Cardiovascular Endpoints

	RSG vs SU OR (95% CI), p-value	RSG vs MET OR (95% CI), p-value
All cardiac ischemic events (serious and nonserious)	1.2 (0.9, 1.6), p=0.2	1.0 (0.8, 1.3), p=0.9
Serious cardiac ischemic events	1.2 (0.8, 1.8), p=0.3	1.0 (0.7, 1.4), p>0.9
CV death, MI or stroke	1.2 (0.7, 1.9), p=0.3	1.1 (0.7, 1.8), p=0.6
CV death	0.6 (0.2, 1.9), p=0.4	1.3 (0.4, 5.0), p=0.7
All-cause mortality	0.5 (0.3, 1.1), p=0.08	0.8 (0.4, 1.8), p=0.7
MI	1.6 (0.8, 3.1), p=0.17	1.3 (0.7, 2.3), p=0.4
Stroke	0.9 (0.4, 2.1), p=0.9	0.8 (0.4, 1.6), p=0.5

Source: Statistical review briefing document by J Mele, DFS 3 Jul 07, Table 4.1.6, pg 22

For all these endpoints, a statistically significant difference between RSG and comparator was not established; 95% confidence intervals for all odds ratios included unity. For RSG vs SU, there was a numerically lower risk of all-cause mortality for RSG, with a p-value of 0.08. Myocardial infarction was associated with a hazard ratio of 1.6 for RSG vs SU, a 95% confidence interval including 1, and a p-value of 0.17.

Ms. Mele also performed subgroup analyses by baseline nitrate and angiotensin converting enzyme inhibitor use; no interaction was noted. However, baseline nitrate use was very infrequent.

Assessment of Cardiovascular Event Coding and Additional Endpoints by FDA Cardiology

Dr. Ellis Unger, an FDA cardiologist and Acting Deputy Director of the Office of Surveillance and Epidemiology, conducted an independent and blinded review of the adverse experiences dataset for ADOPT. The objectives of his review were to examine the appropriateness of coding of cardiovascular adverse event terms, to assign events to a set of endpoints representing clinically meaningful categories of cardiovascular adverse events, and to assess for signals of excess risk within these categories. He analyzed the adverse experiences dataset (ae.xpt) for the ADOPT study. The data set contained 49,695 records. After removal of 2,473 records classified as pre-treatment, he analyzed 47,222 records. All records describing adverse experiences relevant to cardiovascular safety were re-coded. The classification was based on: MedDRA higher level term text, MedDRA lower level dictionary term text, AE enhanced text, MedDRA dictionary synonym, and verbatim term. Each subject was characterized as having experienced or not experienced a given event. Various subgroup explorations were conducted. Dr. Unger's categories include all events, regardless of time relationship to treatment cessation, i.e. events that occurred more than 30 days after cessation of medication are also included. The following table presents the number and percentage of patients in each treatment group who experienced an event within each of the categories defined by Dr. Unger.

Table A32: Number and Percentage of Patients With Events Within Cardiovascular Event Groupings Defined by FDA Cardiology

	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
CHF or pulmonary edema	20 (1.4)	8 (0.6)	17 (1.2)
CHF	17 (1.2)	8 (0.6)	15 (1)
Pulmonary edema	4 (0.3)	2 (0.1)	2 (0.1)
EF decreased, LV dysfunction	3 (0.2)	3 (0.2)	5 (0.3)
Edema, fluid retention	220 (15.1)	138 (9.6)	119 (8.2)
Death	10 (0.7)	5 (0.3)	5 (0.3)
Cardiac arrest; asystole, SCD	1 (0.1)	5 (0.3)	5 (0.3)
Acute MI	29 (2)	18 (1.2)	23 (1.6)
CAD, CHD	104 (7.1)	79 (5.5)	110 (7.6)
CAD, worse; progressive	8 (0.5)	8 (0.6)	11 (0.8)
Myocardial ischemia	4 (0.3)	3 (0.2)	5 (0.3)
Angina	66 (4.5)	45 (3.1)	68 (4.7)
Non-specific ST-T wave changes	3 (0.2)	4 (0.3)	5 (0.3)
ECG C/W ischemia	2 (0.1)	2 (0.1)	3 (0.2)
Unstable angina, ACS, R/O MI	10 (0.7)	9 (0.6)	12 (0.8)
Chest pain, non-cardiac	92 (6.3)	86 (6)	99 (6.8)
PTCA or CABG	5 (0.3)	5 (0.3)	8 (0.6)
PTCA/ PCI	3 (0.2)	2 (0.1)	5 (0.3)
CABG	2 (0.1)	3 (0.2)	3 (0.2)
Vascular disease, PVD	57 (3.9)	59 (4.1)	66 (4.5)
PVD	20 (1.4)	17 (1.2)	10 (0.7)
Aortic stenosis, sclerosis	8 (0.5)	3 (0.2)	5 (0.3)
Hypertension, BP increased	227 (15.6)	260 (18)	310 (21.3)
Hypertensive crisis	3 (0.2)	2 (0.1)	4 (0.3)
Embolism	4 (0.3)	3 (0.2)	2 (0.1)
Pulmonary embolus	4 (0.3)	3 (0.2)	1 (0.1)
DVT	3 (0.2)	3 (0.2)	0 (0)
Thrombophlebitis, phlebitis	21 (1.4)	16 (1.1)	9 (0.6)
Arrhythmia	66 (4.5)	66 (4.6)	65 (4.5)
Tachycardia	19 (1.3)	20 (1.4)	11 (0.8)
Bradycardia	13 (0.9)	8 (0.6)	13 (0.9)
Supra-ventricular	39 (2.7)	36 (2.5)	45 (3.1)
Atrial fibrillation/flutter	27 (1.9)	19 (1.3)	30 (2.1)
Ventricular arrhythmia	8 (0.5)	5 (0.3)	6 (0.4)
VT	0 (0)	0 (0)	1 (0.1)
VF	2 (0.1)	0 (0)	1 (0.1)
PVCs	6 (0.4)	5 (0.3)	4 (0.3)
Conduction disturbance	18 (1.2)	13 (0.9)	23 (1.6)
QRS prolonged, BBB	5 (0.3)	5 (0.3)	14 (1)
AV block	13 (0.9)	8 (0.6)	9 (0.6)
Pre-syncope or syncope	32 (2.2)	24 (1.7)	23 (1.6)
Pre-syncope	10 (0.7)	8 (0.6)	3 (0.2)
Syncope	23 (1.6)	16 (1.1)	21 (1.4)
CVA, TIA, SAH	18 (1.2)	14 (1)	21 (1.4)
SAH	3 (0.2)	2 (0.1)	1 (0.1)

Table A32: Number and Percentage of Patients With Events Within Cardiovascular Event Groupings Defined by FDA Cardiology

	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
CVA	13 (0.9)	12 (0.8)	20 (1.4)
TIA	9 (0.6)	7 (0.5)	11 (0.8)
ICH (not SAH)	4 (0.3)	3 (0.2)	3 (0.2)
Cerebral ischemia (non-stroke)	2 (0.1)	6 (0.4)	4 (0.3)

Source: Dr. Ellis Unger, email 5 Jul 07
Abbreviations: ACS = acute coronary syndrome, AV = atrioventricular, BBB = bundle branch block, BP = blood pressure, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovaseular accident, DVT = deep venous thrombosis, ECG = electrocardiogram, EF = ejection fraction, ICH = intracranial hemorrhage, LV = left ventricular, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, R/O = rule out, SAH = subarachnoid hemorrhage, SCD = sudden cardiac death, TIA = transient ischemic attack, VF = ventricular fibrillation, VT = ventricular tachycardia

The above data are presented as the number of patients who experienced an event within each of the event groupings. The following table, prepared by the clinical reviewer, presents the rate/ 100 PY for events which occurred at a higher frequency in the RSG group than in one of the other treatment groups. This takes into account the lower duration of exposure for patients randomized to SU.

Table A33: Rate/100 PY for Events Within Cardiovascular Event Groupings Defined by FDA Cardiology

	RSG N=1456 PY=4953.8 Rate/100 PY	SU N=1441 PY=4243.6 Rate/ 100 PY	MET N=1454 PY=4905.6 Rate/ 100 PY
CHF or pulmonary edema	0.40	0.19	0.35
CHF	0.34	0.19	0.31
Pulmonary edema	0.08	0.05	0.04
EF decreased, LV dysfunction	0.06	0.07	0.10
Edema, fluid retention	4.44	3.25	2.43
Death	0.20	0.12	0.10
Cardiac arrest; asystole, SCD	0.02	0.12	0.10
Acute MI	0.59	0.42	0.47
CAD, CHD	2.10	1.86	2.24
CAD, worse; progressive	0.16	0.19	0.22
Myocardial ischemia	0.08	0.07	0.10
Angina	1.33	1.06	1.39
Non-specific ST-T wave □s	0.06	0.09	0.10
ECG C/W ischemia	0.04	0.05	0.06
Unstable angina, ACS, R/O MI	0.20	0.21	0.24
Chest pain, non-cardiac	1.86	2.03	2.02
PTCA or CABG	0.10	0.12	0.16
PTCA/ PCI	0.06	0.05	0.10
CABG	0.04	0.07	0.06
Vascular disease, PVD	1.15	1.39	1.35
PVD	0.40	0.40	0.20
Aortic stenosis, sclerosis	0.16	0.07	0.10

Table A33: Rate/100 PY for Events Within Cardiovascular Event Groupings Defined by FDA Cardiology

	RSG N=1456 PY=4953.8 Rate/100 PY	SU N=1441 PY=4243.6 Rate/ 100 PY	MET N=1454 PY=4905.6 Rate/ 100 PY
Hypertension, BP increased	4.58	6.13	6.32
Hypertensive crisis	0.06	0.05	0.08
Embolism	0.08	0.07	0.04
Pulmonary embolus	0.08	0.07	0.02
DVT	0.06	0.07	n/a
Thrombophlebitis, phlebitis	0.42	0.38	0.18
Arrhythmia	1.33	1.56	1.33
Tachycardia	0.38	0.47	0.22
Bradycardia	0.26	0.19	0.27
Supra-ventricular	0.79	0.85	0.92
Atrial fibrillation/flutter	0.54	0.45	0.61
Ventricular arrhythmia	0.16	0.12	0.12
VT	n/a	n/a	0.02
VF	0.04	n/a	0.02
PVCs	0.12	0.12	0.08
Conduction disturbance	0.36	0.31	0.47
QRS prolonged, BBB	0.10	0.12	0.29
AV block	0.26	0.19	0.18
Pre-syncope or syncope	0.65	0.57	0.47
Pre-syncope	0.20	0.19	0.06
Syncope	0.46	0.38	0.43
CVA, TIA, SAH	0.36	0.33	0.43
SAH	0.06	0.05	0.02
CVA	0.26	0.28	0.41
TIA	0.18	0.16	0.22
ICH (not SAH)	0.08	0.07	0.06
Cerebral ischemia (non-stroke)	0.04	0.14	0.08

Source: calculated from Table A32 above

Abbreviations: ACS = acute coronary syndrome, AV = atrioventricular, BBB = bundle branch block, BP = blood pressure, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovascular accident, DVT = deep venous thrombosis, ECG = electrocardiogram, EF = ejection fraction, ICH = intracranial hemorrhage, LV = left ventricular, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, R/O = rule out, SAH = subarachnoid hemorrhage, SCD = sudden cardiac death, TIA = transient ischemic attack, VF = ventricular fibrillation, VT = ventricular tachycardia

From Dr. Unger's cardiovascular event groupings, the following event categories occurred at a frequency ≥1% higher among RSG-treated patients than among SU- or MET- treated patients, or occurred at a rate/100 PY that was ≥0.2 higher for the RSG group than for the SU or MET groups.

Table A34: Cardiovascular Event Groupings From FDA Cardiology Categories that Occurred in ≥1% More Patients in RSG Group than in a Comparator Group; or Events That Occurred at a Rate/ 100 PY that was ≥0.2 Higher for RSG Than for a Comparator

	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
Event Category	**n (%)**	**Rate/ 100 PY**	**n (%)**	**Rate/ 100 PY**	**n (%)**	**Rate/ 100 PY**
Edema, fluid retention	220 (15.1)	4.44	138 (9.6)	3.25	119 (8.2)	2.43
CAD, CHD	104 (7.1)	2.10	79 (5.5)	1.86	110 (7.6)	2.24
Angina	66 (4.5)	1.33	45 (3.1)	1.06	68 (4.7)	1.39
CHF or pulmonary edema events combined	20 (1.4)	0.40	8 (0.6)	0.19	17 (1.2)	0.35
CHF events only	17 (1.2)	0.34	8 (0.6)	0.19	15 (1.0)	0.31
Thrombophlebitis/ phlebitis	21 (1.4)	0.42	16 (1.1)	0.38	9 (0.6)	0.18

Source: Tables A32 and A33 above

Edema and heart failure events occurred more commonly among RSG group patients than among patients in the SU or MET groups. Events within the category "CAD, CHD" occurred with similar frequency in the RSG and MET groups, and at a somewhat lower frequency in the SU group. Per Dr. Unger, this category included all events wherein the occurrence of the event very strongly implies the presence of coronary artery disease. For the category of angina, the frequency pattern of RSG≈MET>SU was also noted.

Overall, Dr. Unger did not note a significant signal for cardiovascular risk within the categories he constructed. He noted that the rate of myocardial infarction appeared low overall, and was not much higher than the rate of stroke. He noted that the rate of MI is often significantly higher than the rate of stroke in large cardiovascular trials, and expressed concern about underascertainment of MI. The clinical reviewer searched for expected rates of strokes and MIs in an early diabetes population, and did not find a population that was entirely analogous to the ADOPT population. In CARDS (Collaborative Atorvastatin Diabetes Study, Colhoun 2004), patients with diabetes and no prior history of cardiovascular disease were included. However, this population was likely at greater cardiovascular risk than the ADOPT population, because all CARDS patients had at least one cardiovascular risk factor in addition to diabetes. In the placebo group in CARDS, 61/1410 patients had a myocardial infarction, and 35 had a stroke. In Dr. Unger's event categorization there were 70 myocardial infarctions among 4351 patients, and 45 strokes. The ratio of stroke to myocardial infarction for both CARDS and ADOPT was 0.6. The rates of MI and stroke in ADOPT were lower than those in the somewhat higher risk population of CARDS, but proportionately so. Myocardial infarctions in ADOPT were not adjudicated, and therefore were not "down-coded" in an adjudication process, which could have resulted in lower numbers. Dr. Unger's coding of events, which included review of verbatim terms, did not identify a concern with inappropriate assignment of event terms. It is unclear whether the rate of MI is lower than expected for this particular diabetic population. This question of underascertainment of MI remains unresolved.

Peripheral Vascular Events

Peripheral vascular events were analyzed separately by GSK, as illustrated in the following table. The clinical reviewer might not have included aortic stenosis or aortic sclerosis as peripheral vascular events. Nevertheless, the incidence of other identified events was low and did not differ between treatment groups.

Table A35: Summary of Peripheral Vascular Events by GSK, Events that Occurred in At Least 2 Patients in Any Treatment Group, Population of All Patients who Received at Least One Dose of Study Medication

	Number of Subjects with AEs of peripheral vascular disease. n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
Preferred Term	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-therapy AEs	36 (2.5)	0.7	31 (2.2)	0.7	27 (1.9)	0.6
Aortic stenosis	6 (0.4)	0.1	2 (0.1)	<0.1	3 (0.2)	0.1
Carotid bruit	4 (0.3)	0.1	3 (0.2)	0.1	4 (0.3)	0.1
Intermittent claudication	4 (0.3)	0.1	2 (0.1)	<0.1	0	0
Carotid artery stenosis	3 (0.2)	0.1	7 (0.5)	0.2	6 (0.4)	0.1
Arterial murmur	2 (0.1)	<0.1	0	0	0	0
Claudication	2 (0.1)	<0.1	4 (0.3)	0.1	3 (0.2)	0.1
Femoral artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	0
Peripheral vascular disease	2 (0.1)	<0.1	5 (0.3)	0.1	3 (0.2)	0.1
Poor peripheral circulation	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.01
Aortic sclerosis	1 (0.1)	<0.1	0	0	2 (0.1)	<0.1
Carotid murmur	1 (0.1)	<0.1	0	0	2 (0.1)	<0.1
Femoral bruit	0	0	2 (0.1)	<0.1	0	0
Subjects with On-therapy SAEs	7 (0.5)	0.1	4 (0.3)	0.1	6 (0.4)	0.1
Aortic stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1
Carotid artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1
Claudication	1 (0.1)	<0.1	0	0	0	0
Arterial occlusion	1 (0.1)	<0.1	1 (0.1)	<0.1	0	0
Vascular stenosis	1 (0.1)	<0.1	0	0	0	0
Arterial occlusive disease	0	0	0	0	1 (0.1)	<0.1
Arterial stenosis	0	0	1 (0.1)	<0.1	0	0
Arterial thrombosis	0	0	1 (0.1)	<0.1	0	0
Ischemic limb pain	0	0	1 (0.1)	<0.1	0	0
Peripheral ischemia	0	0	1 (0.1)	<0.1	0	0
Visceral arterial ischemia	0	0	1 (0.1)	<0.1	0	0
Subjects with On-therapy AEs leading to Withdrawal	0	-	1 (0.1)	-	1 (0.1)	-
Aortic stenosis	0	-	0	-	1 (0.1)	-
Ischemic limb pain	0	-	1 (0.1)	-	0	-

a. Note: Sorted by frequency of adverse events in RSG group.
Data Sources: Table 8.2.4.3, Table 8.2.3.3, Table 8.5.1, and *Ad hoc* Table 1707

Source: ADOPT study report, Table 82, pg 200

Reasons for Withdrawal from Study

A significant percentage of patients withdrew from study for reasons other than monotherapy failure. This, along with the monotherapy failure withdrawals, presents challenges to the evaluation of adverse events. The following table categorizes reasons for withdrawal from the study.

Table A36: Summary of Reasons for Withdrawal by Category of Reason, Population of All Patients Who Received at Least One Dose of Study Medication

	Number of Subjects, n (%)			
On-Therapy (All Randomized Population)	RSG N = 1456	GLY/GLIB N = 1441	MET N = 1454	Total N = 4351
Monotherapy failure not requiring adjudication	102 (7)	243 (16.9)	146 (10.0)	491 (11.3)
Monotherapy failure requiring adjudication	41 (2.8)	68 (4.7)	61 (4.2)	170 (3.9)
Completed without monotherapy failure	692 (47.5)	459 (31.9)	645 (44.4)	1796 (41.3)
Total Withdrawn excluding monotherapy failure	621 (42.7)	671 (46.6)	602 (41.4)	1894 (43.5)
Adverse Event	169 (11.6)	215 (14.9)	178 (12.2)	562 (12.9)
Insufficient therapeutic effect	36 (2.5)	64 (4.4)	53 (3.6)	153 (3.5)
Protocol deviations (including non-compliance)	64 (4.4)	61 (4.2)	51 (3.5)	176 (4.0)
Lost to follow-up	73 (5.0)	79 (5.5)	82 (5.6)	234 (5.4)
Other	279 (19.2)	252 (17.5)	238 (16.4)	769 (17.7)
Withdrew consent	111 (7.6)	110 (7.6)	107 (7.4)	328 (7.5)
Administrative reasons[1]	105 (7.2)	68 (4.7)	68 (4.7)	241 (5.5)
Other	63 (4.3)	74 (5.1)	63 (4.3)	200 (4.6)
On-Therapy prior to first efficacy evaluation				
Withdrawn excluding monotherapy failure	63 (4.3)	104 (7.2)	57 (3.9)	224 (5.1)
Adverse Event	16 (1.1)	54 (3.7)	23 (1.6)	96 (2.2)
Protocol deviations (including non-compliance)	15 (1.0)	17 (1.2)	9 (0.6)	41 (0.9)
Lost to follow-up	9 (0.6)	10 (0.7)	7 (0.5)	26 (0.6)
Other (including withdrawn consent)	20 (1.4)	23 (1.6)	18 (1.2)	61 (1.4)
On-Therapy after first efficacy evaluation (ITT Population)	RSG N = 1393	GLY/GLIB N = 1337	MET N = 1397	Total N = 4127
Monotherapy failure	143 (10.3)	311 (23.3)	207 (14.8)	661 (16.0)
Completed without monotherapy failure	692 (49.7)	459 (34.3)	645 (46.2)	1796 (43.5)
Withdrawn excluding monotherapy failure	558 (40.1)	567 (42.4)	545 (39.0)	1670 (40.5)
Adverse Event	150 (10.8)	161 (12.0)	155 (11.1)	466 (11.3)
Insufficient therapeutic effect	36 (2.6)	64 (4.8)	53 (3.8)	153 (3.7)
Protocol deviations (including non-compliance)	49 (3.5)	44 (3.3)	42 (3.0)	135 (3.3)
Lost to follow-up	64 (4.6)	69 (5.2)	75 (5.4)	208 (5.0)
Other reason (including withdrawn consent)	259 (18.6)	229 (17.1)	220 (15.7)	708 (17.2)

1. Subject did not remain in study until 15MAR2006; not able or unwilling to enter extension, and site closure.

Data Source: Table 6.3.1

Source: ADOPT study report, Table 8, pg 80

Withdrawals due to adverse events were more common among SU group patients than among RSG or MET group patients.

The most common category of reason for non-monotherapy-failure withdrawal was listed as "other". In studies in which a substantial percentage of patients are listed as withdrawing due to "other" reasons, the clinical reviewer routinely examines the verbatim reasons given for withdrawal in order to determine if some withdrawals that were due to adverse events were misclassified as due to "other" reasons. On 18 Jun 07, GSK submitted a full listing of these reasons. The clinical reviewer examined each patient's reason for withdrawal, for all 769 withdrawals due to "other" reasons, and did not find substantial evidence that withdrawals due to adverse events were classified as due to "other" reasons. There was no significant evidence that withdrawals due to cardiovascular events were classified as due to "other" reasons. Most reasons given were typical of administrative withdrawals, e.g. patients moving and sites closing. For ADOPT, many patients chose not to re-consent to participation when the decision was made to amend the protocol and continue the study for longer than the patients had originally consented to participate, and several Institutional Review Boards refused to approve the extension of the study. The following table lists those few reasons listed as "other" that could possibly have been due to an adverse event based on the verbatim reason for withdrawal.

Table A37: Reasons for Withdrawal Listed as "Other" That Could Possibly Have Been Classified as Due to an Adverse Event, Population of All Randomized Patients

Verbatim Reason for Withdrawal	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)	TOTAL N=4351 n (%)
"Withdrew consent" multiple stress (situational) and fears about study medication (sic)	1 (0.4)			1 (0.1)
Patient self-withdrew consent was unhappy with treatment and due to anxiety (sic)	1 (0.4)			1 (0.1)
Alcohol abuse			1 (0.4)	1 (0.1)
Cardiac valve operation in near future	1 (0.4)			1 (0.1)
Creatinine >1.4 mg/dL not an AE, investigator decision (sic)			1 (0.4)	1 (0.1)
Decision of investigator due to liver enzymes elevated		1 (0.4)		1 (0.1)
Heart insufficiency – no AE as discussed with SB Harlow by Oliver Kaikante (sic)		1 (0.4)		1 (0.1)
Hypoglycemia in the post (sic) with study medications		1 (0.4)		1 (0.1)
Hypoglycemias (sic) episodes		1 (0.4)		1 (0.1)
Intolerability to study drug (sic)		1 (0.4)		1 (0.1)
Investigator's discretion but pt unwilling to increase to DL 4 due to intolerable gastrointestinal side effects at DL3	1 (0.4)			1 (0.1)
Patient experienced some symptoms which are related to the medication but which could have resulted from gastroenteritis (patient chose to leave trial)			1 (0.4)	1 (0.1)
Patient stressed by other factors and aggravated by insomnia which he feels is related to study meds? (sic)		1 (0.4)		1 (0.1)
Possible liver toricities (sic) due to methotrexate			1 (0.4)	1 (0.1)
Principal investigator felt best to withdraw pt. due to decline in health status	1 (0.4)			1 (0.1)
Pt felt diabetic neuropathy worsened on study medication	1 (0.4)			1 (0.1)
The patient is sure of the treatment is responsible for GGT increase (sic)		1 (0.4)		1 (0.1)
The patient was withdrawn from study medication due to the complexity of associated pathologies and multiple treatment (sic) the patient has recently received (investigator's decision)			1 (0.4)	1 (0.1)
Tolerance problems		1 (0.4)		1 (0.1)
Unable to tolerate study drug		1 (0.4)		1 (0.1)

Source: NDA 21071 SE8 026 submission 18 Jun 07, Ad-hoc Table 1995, pages 1-14

Overall, these reasons do not indicate a significant problem with misclassification of reasons for withdrawal. These few reasons, even if added to adverse event data, would not change the distribution of adverse event withdrawals among the treatment groups.

The following table presents cardiovascular adverse events which led to withdrawal from study. The clinical reviewer included all terms which could potentially represent cardiovascular events; some terms are not specific and may represent non-cardiovascular events.

Table A38: Cardiovascular Adverse Events Which Led to Withdrawal from Study

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
Cardiac disorders	Any	24 (1.6)	12 (0.8)	18 (1.2)
	Acute coronary syndrome	0	1 (0.1)	1 (0.1)
	Acute myocardial infarction	1 (0.1)	2 (0.1)	0
	Angina pectoris	2 (0.1)	2 (0.1)	1 (0.1)
	Angina unstable	1 (0.1)	0	1 (0.1)
	Arrhythmia	0	1 (0.1)	0
	Atrial fibrillation	0	2 (0.1)	1 (0.1)
	Atrial flutter	0	1 (0.1)	0
	Bradycardia	0	1 (0.1)	0
	Cardiac arrest	0	0	2 (0.1)
	Cardiac failure	4 (0.3)	1 (0.1)	2 (0.1)
	Cardiac failure acute	2 (0.1)	0	0
	Cardiac failure congestive	1 (0.1)	3 (0.2)	2 (0.1)
	Cor pulmonale	1 (0.1)	0	0
	Coronary artery disease	1 (0.1)	1 (0.1)	3 (0.2)
	Ischemic cardiomyopathy	1 (0.1)	0	0
	Left ventricular failure	0	0	1 (0.1)
	Mitral valve disease	1 (0.1)	0	0
	Myocardial infarction	7 (0.5)	3 (0.2)	4 (0.3)
	Myocardial ischemia	0	0	1 (0.1)
	Palpitations	1 (0.1)	0	0
	Pericardial calcification	1 (0.1)	0	0
	Right ventricular failure	1 (0.1)	0	0
	Ventricular dyskinesia	1 (0.1)	0	0
	Ventricular tachycardia	0	0	1 (0.1)
General disorders and administration site conditions	Any (CV or non-CV)	25 (1.7)	17 (1.2)	10 (0.7)
	Chest pain	1 (0.1)	0	0
	Edema	1 (0.1)	0	0
	Edema face	1 (0.1)	0	0
	Edema generalized	3 (0.2)	0	0
	Edema peripheral	12 (0.8)	5 (0.3)	4 (0.3)
	Edema pitting	1 (0.1)	0	0
	Sudden death	0	1 (0.1)	0
Investigations	Any (CV or non-CV)	33 (2.3)	24 (1.7)	25 (1.7)
	Electrocardiogram PQ interval prolonged	1 (0.1)	0	0
Metabolism and nutrition disorders	Any (CV or non-CV)	14 (1.0)	101[1] (7.0)	25 (1.7)
	Fluid retention	1 (0.1)	0	1 (0.1)
Nervous system disorders	Any (CV or non-CV)	15 (1.0)	17 (1.2)	9 (0.6)
	Cerebral infarction	0	0	1 (0.1)
	Cerebrovascular accident	5 (0.3)	4 (0.3)	3 (0.2)
	Hemiparesis	0	0	1 (0.1)
	Subarachnoid hemorrhage	0	1 (0.1)	1 (0.1)
	Syncope	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Any (CV or non-CV)	8 (0.5)	9 (0.6)	0
	Acute pulmonary edema	1 (0.1)	0	0

Table A38: Cardiovascular Adverse Events Which Led to Withdrawal from Study

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
	Dyspnea	3 (0.2)	1 (0.1)	0
	Dyspnea exertional	0	2 (0.1)	0
	Pulmonary edema	0	1 (0.1)	0
Vascular disorders	Any	2 (0.1)	3 (0.2)	2 (0.1)
	Aortic dissection	0	0	1 (0.1)
	Aortic stenosis	0	0	1 (0.1)
	Hypertension	1 (0.1)	1 (0.1)	0
	Hypotension	0	1 (0.1)	0
	Ischemic limb pain	0	1 (0.1)	0
	Varicose vein	1 (0.1)	0	0

Source: ADOPT study report, Table 8.5, beg pg 4238
1 For SU, 70 withdrawals due to hypoglycemia and 24 withdrawals due to hyperglycemia

For the terms acute myocardial infarction or myocardial infarction, there were 8, 5 and 4 withdrawals for the RSG, SU and MET groups respectively. Withdrawals due to heart failure or edema were more common among RSG-treated patients than among patients in the SU or MET groups.

Other Notable Safety Findings

As might be expected with an insulin secretagogue, sulfonylurea treatment was associated with a substantially higher incidence of hypoglycemic events, and withdrawals due to hypoglycemia, as illustrated in the following table.

Table A39: Summary of Hypoglycemic Events, Population of All Patients Who Received at Least One Dose of Study Medication

Preferred Term / Lower Level Term	Number of subjects with hypoglycemic events, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-therapy AEs	142 (9.8)	2.9	557 (38.7)	13.1	168 (11.6)	3.4
Hypoglycemia	128 (8.8)	2.6	510 (35.4)	12.0	148 (10.2)	3.0
Hypoglycemic episode	13 (0.9)	0.3	76 (5.3)	1.8	22 (1.5)	0.4
Blood sugar decreased	3 (0.2)	0.1	3 (0.2)	0.1	0	0
Hypoglycemic reaction	2 (0.1)	<0.1	3 (0.2)	0.1	2 (0.1)	<0.1
Hypoglycemia aggravated	1 (0.1)	<0.1	0	0	1 (0.1)	<0.1
Plasma glucose decreased	1 (0.1)	<0.1	0	0	0	0
Blood glucose decreased	0	0	4 (0.3)	0.1	0	0
Fasting blood glucose decreased	0	0	2 (0.1)	0.1	0	0
Glucose decreased	0	0	2 (0.1)	0.1	0	0
Hypoglycemia night	0	0	3 (0.2)	0.1	0	0
Subjects with On-therapy SAEs[1]	1 (0.1)	<0.1	8 (0.6)	0.2	1 (0.1)	<0.1
Subjects with On-therapy AEs leading to Withdrawal	0	-	70 (4.9)	-	5 (0.3)	-
Hypoglycemia	0	-	66 (4.6)		5 (0.3)	-
Hypoglycemic episode	0	-	4 (0.3)	-	0	-

1. All SAEs were coded to the lower level term of hypoglycemia.
a. Note: Sorted by frequency of adverse events in RSG group.
Data Sources: Table 8.2.4.3, Table 8.2.3.3, Table 8.5.1, and *Ad hoc* Table 1707

Source: ADOPT study report, Table 85, pg 202

The incidence and time course of occurrence of hypoglycemic events was similar for RSG and MET, as illustrated in the following time-to-event analysis and Kaplan-Meier curves.

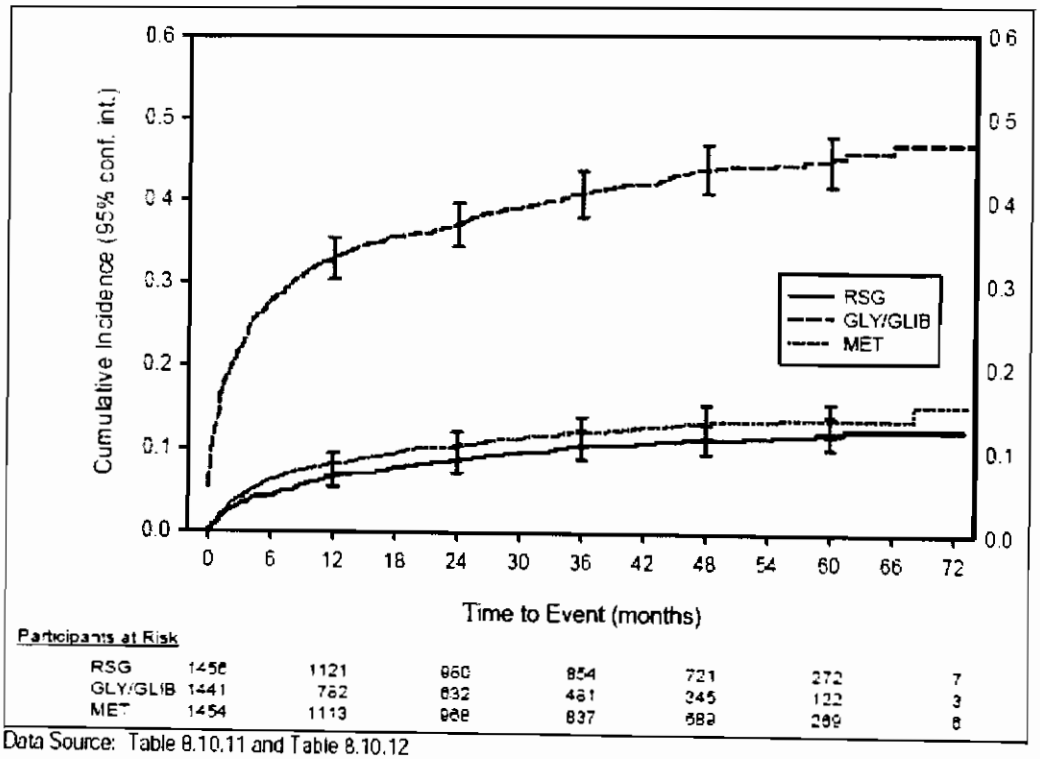
Table A40: Analysis of Time-to-First Hypoglycemic Adverse Event, Population of All Patients Who Received at Least Onc Dose of Study Medication

Hypoglycemia	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Subjects with event during study, n	142	557	168
60-month Cumulative Incidence (95% CI)	0.12 (0.10, 0.14)	0.45 (0.42, 0.48)	0.14 (0.12, 0.16)
RSG vs. Control			
Hazard ratio (95% CI)	-	0.195 (0.162, 0.234)	0.838 (0.670, 1.047)
p-value	-	<0.0001	0.1204

Data Sources: Table 8.10.15 and Table 8.10.17

Source: ADOPT study report, Table 86, pg 203

Figure A16: Cumulative Incidence of First Hypoglycemic Adverse Event, Population of All Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 55, pg 203

Bladder Neoplasms

The other approved thiazolidinedione, pioglitazone, is associated with bladder tumors in animals and humans. In ADOPT, for whieh rosiglitazone was the TZD under study, the incidence of bladder neoplasms was low and did not differ between treatment groups.

Table A41: Incidence of Bladder Neoplasms, Population of All Patients Who Received at Least One Dose of Study Medication

Event	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Bladder cancer	2 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1
Bladder neoplasm	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1
Bladder papilloma	0	n/a	0	n/a	1 (0.1)	<0.1

Source: ADOPT study report, Table 8.2.3.1, beg pg 4037

Data from both ADOPT (rosiglitazone) and PROactive (pioglitazone) were consistent with an increased incidence of fracture among women. These tended to be extremity fractures, rather than vertebral or hip fractures. Both sponsors have agreed to place information in their product labels regarding this safety finding, and both have widely sent Dear Healthcare Provider letters informing physieians of this concern.

"MACE" (Major Adverse Cardiovascular Events) Composite Endpoint Post Hoc Analyses

As the results of the FDA meta-analysis of diabetes trials began to support an increased short-term risk of myocardial ischemic events with rosiglitazone, the FDA began to explore methods of further assessing this signal. The usual practice after a meta-analysis of small trials suggests a safety concern is to search for larger, longer term trials that one can use to see if the finding is consistent. A significant issue in this process is the desire to examine similar endpoints across data sources, so that one can "compare apples to apples", if possible. This can be a very difficult process, because adverse event data across different trials may be collected and adjudicated in different ways. In large cardiovascular outcome trials, composite endpoints are often used which contain individual endpoints which are felt to be important serious events for which there is a relatively good likelihood that the assigned event term actually represents the event in question. One endpoint that is commonly used in cardiovascular outcome trials is a composite of cardiovascular death, myocardial infarction and stroke. After discussions with the FDA regarding the desirability of utilizing a common endpoint across data sources, GSK performed analyses utilizing a composite of cardiovascular death, serious adverse events of myocardial infarction, and serious adverse events of stroke. Events for this endpoint were ascertained by use of the same unadjudicated SAE terms that had been used by GSK for their CV AE groupings analyses. For cardiovascular deaths, non-CHF deaths were included, and were identified as deaths occurring due to an SAE that had a MedDRA Lower Level Term within the set of non-CHF cardiovascular events that were prespecified for the ADOPT CV event groupings (source, NDA 21071 SE8 022, 31 May 07 submission, pages 52-77).

The following table summarizes GSK's analyses of CV safety in ADOPT using this endpoint.

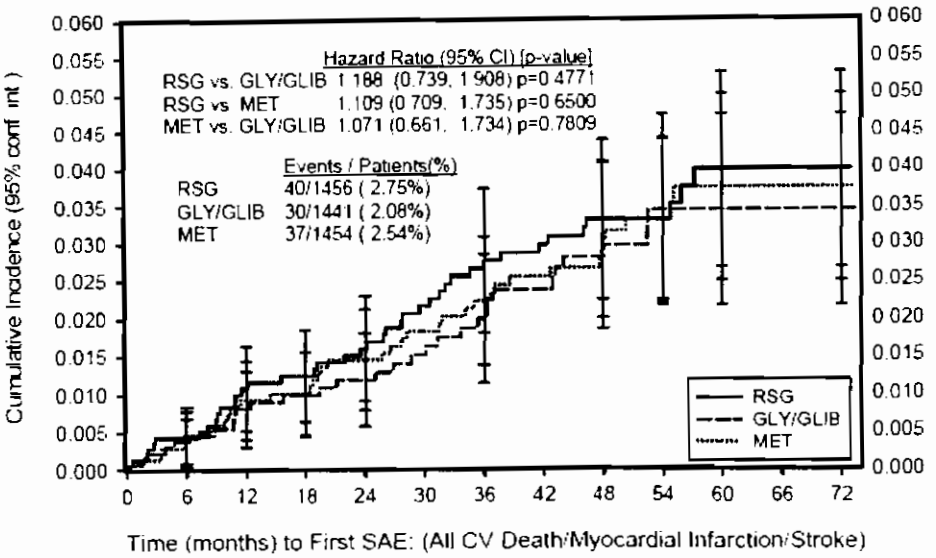
Table A42: Analysis of "MACE" Composite and Components in ADOPT ("MACE" = Endpoint of Cardiovascular Mortality, Serious Adverse Events of Myocardial Infarction [Fatal or Nonfatal] and Serious Adverse Events of Stroke [Fatal or Nonfatal])

Endpoint	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		Comparison	HR (95% CI)	p-value
	# events (%)	Rate/ 100 PY	# events (%)	Rate/ 100 PY	# events (%)	Rate/ 100 PY			
MACE	40 (2.75)	0.81	30 (2.08)	0.71	37 (2.54)	0.75	RSG vs MET	1.109 (0.709, 1.735)	0.6500
							RSG vs SU	1.188 (0.739, 1.908)	0.4771
							MET vs SU	1.071 (0.661, 1.734)	0.7809
CV Mortality	5 (0.34)	0.10	8 (0.56)	0.19	4 (0.28)	0.08	RSG vs MET	1.304 (0.350, 4.859)	0.6929
							RSG vs SU	0.582 (0.190, 1.783)	0.3429
							MET vs SU	0.446 (0.134, 1.484)	0.1881
Myocardial Infarction SAE	24 (1.65)	0.48	14 (0.97)	0.33	20 (1.38)	0.41	RSG vs MET	1.227 (0.677, 2.221)	0.5004
							RSG vs SU	1.518 (0.785, 2.938)	0.2149
							MET vs SU	1.238 (0.625, 2.453)	0.5407
Stroke SAE	13 (0.89)	0.26	12 (0.83)	0.28	17 (1.17)	0.35	RSG vs MET	0.773 (0.376, 1.593)	0.4860
							RSG vs SU	0.944 (0.430, 2.071)	0.8849
							MET vs SU	1.220 (0.582, 2.557)	0.5986

Source: NDA 21071 SE8 022 submission from 31 May 07, analyses Table 4, pg 9

The following Kaplan-Meier curves illustrate the cumulative incidence of events from this composite endpoint in ADOPT.

Figure A17: Cumulative Incidence of Composite of Cardiovascular Mortality, Serious Myocardial Infarction, and Serious Stroke



Participants at Risk

RSG	1456	1197	1067	945	799	310	8
GLY/GLIB	1441	1108	956	779	600	214	7
MET	1454	1199	1069	941	779	306	8

Source: NDA 21071 subm dated 31 May 07, Figure 3, pg 10

For this combined endpoint, with the ascertainment methods used by GSK, there was little difference between treatment groups for the composite. This endpoint, and all other cardiovascular endpoints which have been used for ADOPT and for the pooled diabetes studies meta-analyses, are post hoc and subject to weaknesses related to retrospective analyses. As discussed earlier, detailed review of ascertainment is continuing.

Limitations of Study With Respect to Interpretation of Cardiovascular Safety Data

All clinical trials have limitations, which must be considered during review. The following are some of the limitations of ADOPT with respect to interpretation of cardiovascular safety data.

- This was an efficacy and general safety trial, and was not specifically designed as a cardiovascular safety trial; there were no predefined cardiovascular endpoints.
- There was a high withdrawal rate, both for failure of monotherapy and for non-monotherapy-failure reasons.
- As a result of greater withdrawal rates for sulfonylurea group patients, there was greater exposure for rosiglitazone and metformin than for sulfonylurea, confounding the interpretation of events per arm. Time-to-event analyses, and consideration of rates by patient-year, can somewhat address this issue, but questions of the effect of the high withdrawal rate remain.
- An active comparator design was used; if comparator agents themselves have an adverse effect on cardiovascular safety, this may obscure cardiovascular effects of rosiglitazone.
- Adverse events were only routinely ascertained out to 30 days after cessation of study medication. This is common in clinical trials, but because patients were expected to withdraw from this study due to monotherapy failure, it would have been desirable to continue to follow patients for a longer period after study medication cessation.

- Lipids and blood pressure were not intensively managed in order to equalize these risk factors, and differences were present at endpoint for these cardiovascular risk factors, as well as for HbA1c. Differences in these values at endpoint create difficulty in true comparison of cardiovascular risk, which is often highly dependent on traditional risk factors. The contribution of these traditional risk faetors may outweigh any independent contribution of the drug in question.
- Patients had early diabetes at entry, and were perhaps at lower risk for cardiovascular events than an average type 2 diabetic population. This might impact generalizability of any conclusions to a broader use population.
- Predefined adjudication of cardiovascular events did not occur; use of investigator terms and/or Preferred Terms may not correlate perfectly with adjudicated terms.
- Lower Level MedDRA terms were used to construct groupings of cardiovascular event terms; use of these terms rather than Preferred Terms complicates verification of inclusiveness.
- The post hoc cardiovascular endpoints for ADOPT were not identical to the endpoints used in the retrospective meta-analysis of pooled diabetes studies. While some relatively well-accepted composite cardiovascular endpoints exist that may allow one to look at similar endpoints for these and other sources of cardiovascular safety data for rosiglitazone, one must recognize that differences between trials may result in differences in the exact events included in these composites. A single, or even several, composite endpoints, used across data sources, may not fully characterize cardiovascular safety.
- Small numbers of cardiovascular events increase uncertainty of estimates; many estimates are therefore unstable, and only a few added events in one group or another could significantly change the estimates.

Strengths of ADOPT

- The duration of ADOPT was much longer than the mean duration of trials in the pooled diabetes studies included in the meta-analysis.
- ADOPT had a large number of patients.
- Because ADOPT was a single study, issues of between-study heterogeneity, which are important in meta-analyses, were not relevant.
- Because ADOPT was a single study, randomization could be maintained for adverse event analyses.
- Baseline risk factors and other characteristics were generally well-matched between treatment groups.
- While a comparison to placebo is useful in characterization of absolute event rates, real-world management of diabetes does not usually involve choosing between one drug or no drug at all. The choice is usually between one drug and another drug of a different class. In ADOPT, active comparison of rosiglitazone to sulfonylurea or metformin was more relevant to the types of treatment decisions often faced by physicians who treat diabetes.

Summary of Cardiovascular Safety Findings from Ongoing Clinical Review of ADOPT

As of the writing of this briefing document, the findings of the cardiovascular safety review of ADOPT include:

- A large percentage of patients withdrew from study, both due to reaching the primary endpoint of monotherapy failure, and due to non-monotherapy failure reasons. The withdrawal rate was higher in the SU group, and the exposure was lower in this group. The issues of high withdrawal and differential exposure neeessitate caution in interpretation of CV safety data.
- Glycemic control, blood pressure values, and lipid values were statistically significantly different between treatment groups at 48 months. Ideally, one would wish for cardiovascular risk factors

to be similar at endpoint, so that one could assess the independent CV effect of a drug, with all other significant risk factors being roughly equal.

- Total mortality across the entire course of study was similar between treatment groups. When considering deaths that occurred during the adverse event ascertainment period of the study (out to 30 days after cessation of treatment), total mortality occurred at rates/ 100 PY of 0.2, 0.5, and 0.1 for the RSG, SU, and MET groups, respectively. In a time-to-event analysis by FDA Biometrics, the odds ratio for total mortality for RSG vs SU was 0.5 (95% CI 0.3, 1.1; p-value 0.08).
- The incidence of cardiovascular death was low, and was not significantly different between treatment groups.
- Total MedDRA Cardiovascular System Organ Class events occurred with similar frequency among patients in the RSG and MET treatment groups, and with somewhat lower frequency among patients in the SU group.
- Total MedDRA Vascular System Organ Class events occurred with similar frequency in patients in each of the treatment groups.
- Out of some 240 cardiovascular adverse event MedDRA Preferred Terms which occurred in any patient in ADOPT, few individual cardiovascular adverse event terms were reported with greater frequency among RSG group patients than among patients in the SU and MET groups. The individual serious adverse event term "myocardial infarction" (not including other myocardial ischemic event terms such as "acute myocardial infarction") occurred at rates/100 PY of 0.4, 0.2 and 0.3 for RSG, SU and MET group patients, respectively. When considering all adverse event terms (serious and nonserious), adverse event terms of edema and dyspnea were reported more frequently among RSG group patients than among MET or SU group patients. The single term "syncope" was reported at rates/100 PY of 0.4, 0.2 and 0.3 for RSG, SU and MET group patients, respectively.
- Consideration of individual event terms does not allow for full characterization of events within categories of cardiovascular events. In event grouping analyses performed by GSK, rates of total myocardial ischemic events and total arrhythmia events did not differ significantly between treatment groups. Heart failure and pulmonary edema events occurred with similar frequency in the RSG and MET groups, but occurred at a lower frequency in the SU group. There was also a group of "other" cardiovascular adverse events, for which there was no significant differenee between treatment groups. Examination of GSK's assignment of event terms to groupings did not reveal significant inappropriate assignment of terms to the "other CV events" category. Examination of the inclusiveness of the event groupings is ongoing as a search for lack of ascertainment; this process will require reconciliation of assignment of thousands of events. Thus far, this search has not revealed evidence of omission of important cardiovascular events from groupings.
- FDA Biometrics also performed time-to-event analyses for multiple endpoints involving adverse cardiovascular events. These included all-cause mortality, cardiovascular mortality, stroke, all cardiac ischemic events and all serious cardiac isehemic events. A composite of CV death, MI and stroke was also analyzed. A statistieally significant difference between RSG and comparator was not established for any of these endpoints. For all-eause mortality, the odds ratio for RSG vs SU was 0.5 (95% CI 0.3, 1.1), favoring RSG, with a p-value of 0.08. For myocardial infarction, the odds ratio for RSG vs SU was 1.6 (95% CI 0.8, 3.1), with a p-value of 0.17. For comparisons of RSG to MET, no p-values approached statistical signifieance.
- An independent and blinded review of all adverse event terms (>49,000 records) in the ADOPT adverse event database was conducted by Dr. Ellis Unger, an FDA cardiologist and Acting Deputy Director of the Offiee of Surveillance and Epidemiology. His objective was to assess the appropriateness of coding of cardiovascular adverse events, to assign events to a set of endpoints representing clinically meaningful categories of cardiovascular events, and to assess for signals of excess risk within these categories. His review did not reveal evidence of significant miscoding

of CV events, and did not reveal a significant signal of excess risk within his endpoint categories. He did note a relatively low incidence of myocardial infarction overall, and raised a concern about possible underascertainment.

- Withdrawals from study due to adverse events of heart failure or edema were more common among RSG group patients than among comparator group patients. For the terms "acute myocardial infarction" and "myocardial infarction" there were a total of 8, 5 and 4 withdrawals for the RSG, SU and MET groups, respectively. Withdrawals from study due to any adverse event were more common among SU group patients than among the other treatment group patients; this excess was largely due to hypoglycemia.
- Limitations of ADOPT with regard to assessment of cardiovascular safety are discussed above.
- Overall, ADOPT does not appear to present a significant signal of excess myocardial ischemic event risk, of excess total mortality, or of excess cardiovascular mortality, for RSG vs SU or MET. Conversely, ADOPT's results also cannot provide complete reassurance of a lack of excess cardiovascular risk; it is difficult for any clinical trial to "clear" a drug of a signal of increased risk.

DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)
Status: This study was not conducted or analyzed by GSK. Results were analyzed by the Population Health Research Institute at McMaster University. The completed trial results for rosiglitazone (separately from the ramipril findings) were published in *Lancet* September 2006 by the independent DREAM investigators. The FDA does not have access to the full clinical datasets for this trial.

Study Design and Study Objectives: This was a multi-center, multi-national, double-blind, randomized, placebo-controlled clinical trial of patients with impaired fasting glucose or impaired glucose tolerance. Patients were randomized to ramipril 15 mg/day or placebo and rosiglitazone 8 mg/day or placebo in a 2x2 faetorial design and assessed semi-annually for the primary composite endpoint of incident diabetes or death. Death was included to account for the association between diabetes and mortality and to avoid the problem of competing risk (i.e., diabetes may develop at a different rate in individuals who die than in individuals who do not).

Incident diabetes was ascertained based on any of the following:

- locally measured fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or greater or 2 hr plasma glucose concentration of 11.1 mmol/L (200 mg/dL) or greater during a 75 g OGTT that was confirmed by another test on a different day
- a single test eonsistent with diabetes without reason for exclusion of diagnosis based on blinded adjudicator assessment
- physician diagnosed diabetes outside of the study that was supported by the prescription of an antidiabetic agent and either a FPG > 7.0 mmol/L or any glucose level > 11.1 mmol/L

Secondary outcomes included: regression to normal fasting and 2hr post-prandial glucose concentrations; a composite of CV events (MI, stroke, CV death, revascularization procedures, heart failure, new angina with objective evidence of ischemia, or ventricular arrhythmia requiring resuscitation); individual components of the CV composite; renal events and a composite cardiorenal outcome; and glucose concentrations. Clinical outcomes were adjudicated by a committee blinded to study treatment assignment.

The predicted incidence of the primary outcome in this population was 4.5% or greater per year. A sample size of at least 5000 patients was estimated to provide 90% power to detect a minimum 22% risk reduetion attributable to either ramipril or rosiglitazone.

Patient Population
DREAM enrolled patients at risk for developing diabetes based on fasting and challenged glucose levels. Sinee this trial is evaluating the effect of a therapy on preventing diabetes, it is reasonable to assume that the study population is at lower risk for a cardiovascular event than other studies enrolling patients with established diabetes mellitus. And by definition, this population is also referred to as treatment-naïve. Limiting enrollment to a low risk CV population is further achieved by specific exclusion criteria (e.g., CV disease including EF < 40% or CHF or prior MI or stroke, renal or hepatie disease). Current use of an ACE-inhibitor was also an exclusion criterion.

A total of 24,872 individuals were screened and 5269 were randomized to the following treatment groups: 1321 placebo; 1325 rosiglitazone monotherapy; 1313 ramipril monotherapy; 1310 rosiglitazone + ramipril. In the *Lancet* publication, the treatment groups were collapsed into two comparison groups: rosiglitazone-containing treatment groups versus the ramipril monotherapy/placebo groups. The latter group was referred to as the placebo group. The following table summarizes certain baseline charaeteristics and demographics of the study population as presented in the *Lancet* publication.

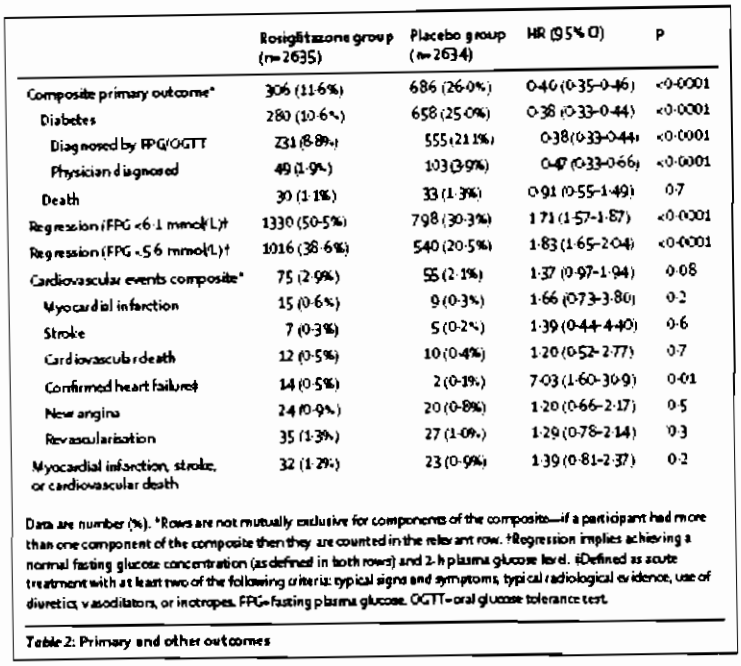
Table D1: Selected Baseline Characteristics and Demographics of DREAM Study Participants		
	Rosiglitazone N=2635	**Placebo N=2634**
Mean age (yrs)	54.6	54.8
Women	58.3%	60.1%
Medical history		
History of HTN	44.0%	43.0%
Current or former tobacco use	43.9%	45.3%
> 3 ETOH drinks/wk	21.1%	19.1%
Baseline Meds		
ASA/antiplatelcts	14.4%	14.3%
Thiazide diuretics	9.3%	10.1%
Other diuretics or aldosterone antagonists	6.0%	5.5%
Angiotensin receptor blocker	5.8%	5.1%
Beta-blocker	17.8%	16.8%
Calcium channel blocker	12.5%	13.3%
Statin/fibrate	14.8%	14.8%
Mean BMl (kg/m2)	30.8	31.0

The DREAM population is obviously different from the patients contributing data to the meta-analysis which combined studies in patients with *established* T2DM. With respect to baseline CV risk, patients who are naïve to drug therapy in the meta-analysis are likely to be a more comparable patient population to DREAM than the previously-treated patients.

Study Outcome

The median follow-up was 3.0 years. The following table is from the *Lancet* September 2006 publication which summarizes the primary and secondary outcomes.

Table D2: Primary and Secondary Outcomes in DREAM



	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	P
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·46)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7
Regression (FPG <6·1 mmol/L)†	1330 (50·5%)	798 (30·3%)	1·71 (1·57–1·87)	<0·0001
Regression (FPG <5·6 mmol/L)†	1016 (38·6%)	540 (20·5%)	1·83 (1·65–2·04)	<0·0001
Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Data are number (%). *Rows are not mutually exclusive for components of the composite—if a participant had more than one component of the composite then they are counted in the relevant row. †Regression implies achieving a normal fasting glucose concentration (as defined in both rows) and 2-h plasma glucose level. ‡Defined as acute treatment with at least two of the following criteria: typical signs and symptoms, typical radiological evidence, use of diuretics, vasodilators, or inotropes. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

Table 2: Primary and other outcomes

The rosiglitazone-containing treatment group had a significantly lower incidence of developing either diabetes or experiencing death compared to the placebo group (primary outcome measure). The predominant event in this primary composite endpoint was incidence of diabetes with 10.6% of rosiglitazone-treated patients developing diabetes compared to 25.0% of placebo-treated patients. There was essentially no difference between the two treatment groups in overall mortality (1.1% rosiglitazone vs. 1.3% placebo).

Concern has been raised regarding the secondary composite of CV events. There was a non-significant increase in the composite endpoint of MI, stroke, CV death, heart failure, angina, or revascularization (HR 1.37; 95% CI: 0.97-1.94) with a statistically significant difference in the incidence of heart failure (HR 7.03; 95% CI: 1.60-30.9). Heart failure is a known, dose-related side-effect of TZDs. In is therefore important to note that DREAM studied the highest approved dose of rosiglitazone "*to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose.*" For the commonly combined cardiovascular endpoints of MI, stroke, and CV death, there was a non-significant increase associated with rosiglitazone treatment (1.2%) compared to placebo (0.9%) (HR 1.39; 95% CI: 0.81-2.37). This HR is very similar to that seen in the GSK meta-analysis.

However, as noted earlier, the results summarized in the September 2006 publication combined the factorial groups into rosiglitazone- versus non-rosiglitazone-containing treatment groups. The results of ramipril were published separately in the *New England Journal of Medicine* in October 2006.[1] A letter to the *Lancet* by Lubson and Poole-Wilson questioned the choice of presenting these data in aggregated groupings, rather than by individual treatment cells.[2] The following table summarizes the CV outcomes by factorial group, as provided by the DREAM investigators to the FDA.

[1] The Dream Trial Investigators. Effect of Ramipril on the incidence of diabetes. *N Engl J Med* 2006; 355:1551-1562.
[2] Lubson J and Poole-Wilson PA. Letter to editor. *Lancet* 2006; 368:2050.

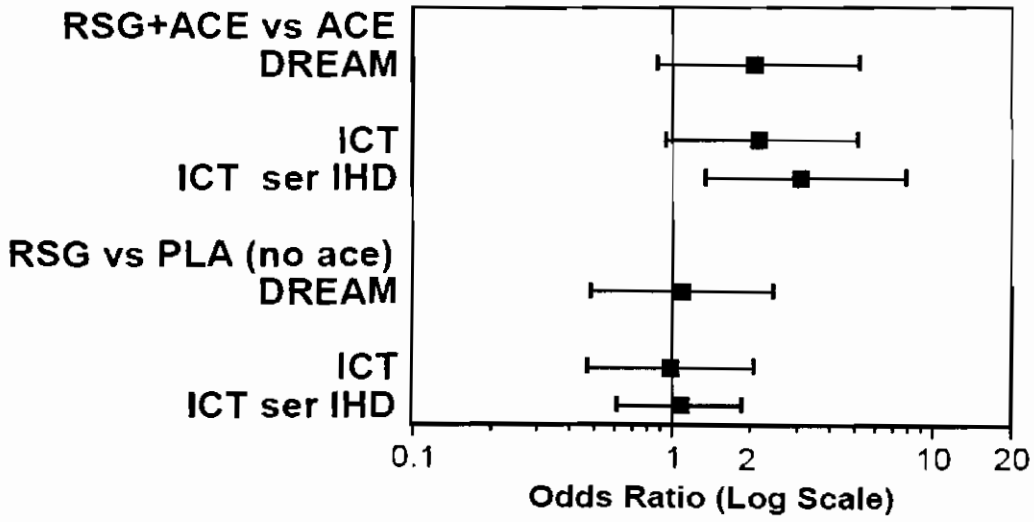
Table D3: CV Outcomes in DREAM Presented by Factorial Groups

	Ramipril+Rosiglitazone N=1310		Ramipril Only N=1313		Rosiglitazone Only N=1325		Placebo N=1321	
	N	%	N	%	N	%	N	%
CV Composite	45	3.4	24	1.8	32	2.4	32	2.4
MI	11	0.8	3	0.2	5	0.4	6	0.5
Stroke	2	0.2	2	0.2	5	0.4	3	0.2
All Death	15	1.1	16	1.2	15	1.1	17	1.3
CV Death	7	0.5	5	0.4	5	0.4	5	0.4
Revasc	18	1.4	10	0.8	19	1.4	19	1.4
New Angina	15	1.1	9	0.7	9	0.7	11	0.8
CHF	11	0.8	1	0.1	3	0.2	1	0.1

In this analysis, the incidences of the CV composite and the individual components of this composite are similar between patients treated with rosiglitazone and placebo-treated patients. Ramipril-only treated patients had an overall lower rate of CV events compared to both rosiglitazone- and placebo-groups (a finding reflective of the CV prevention indication for ramipril). An unexpected finding was an increased risk of CV events in the treatment group receiving *both* ramipril and rosiglitazone. The DREAM investigators stated in the author's reply that no statistical interaction between the two interventions were observed (p=0.11). In the information provided to the FDA, tests for interaction between the two treatments were significant for the CV composite (p=0.066) and MI (p=0.09). As diseussed in Ms. Mele's review of the meta-analysis, there were 5,126 reported users and 9,670 non-users of ACE-inhibitors across the 42 controlled clinical trials. The odds ratio for ischemie heart disease was statistically signifieantly increased among the users (1.8; p=0.009) whereas the increase among non-users was not significant (1.3; p=0.18). In Figure 4.2.3 of Ms. Mele's memo, she further compares the DREAM cohort to the subgroup of placebo-controlled studies from the meta-analysis (selection of placebo-only was because DREAM was a placebo-controlled study) with respect to use or non-use of ACE-inhibitor. Although this is an exploratory analysis, the point estimates and the Cls around these estimates for the composite of CV death, MI, and stroke and the serious ischemic heart disease are nearly superimposable between these two clinical databases, and would argue that further investigation in the combined effects of rosiglitazone (and perhaps all TZDs) and ACE-inhibitors are warranted.

The following figure is obtained from Ms. Mele's briefing memo to the advisory committee.

Figure 4 2.3 Plot of odds ratios for the combination of RSG with an ACE inhibitor in DREAM and in the database of short-term studies for the composite endpoint of CV death, MI or stroke and for serious ischemic (IHD) events



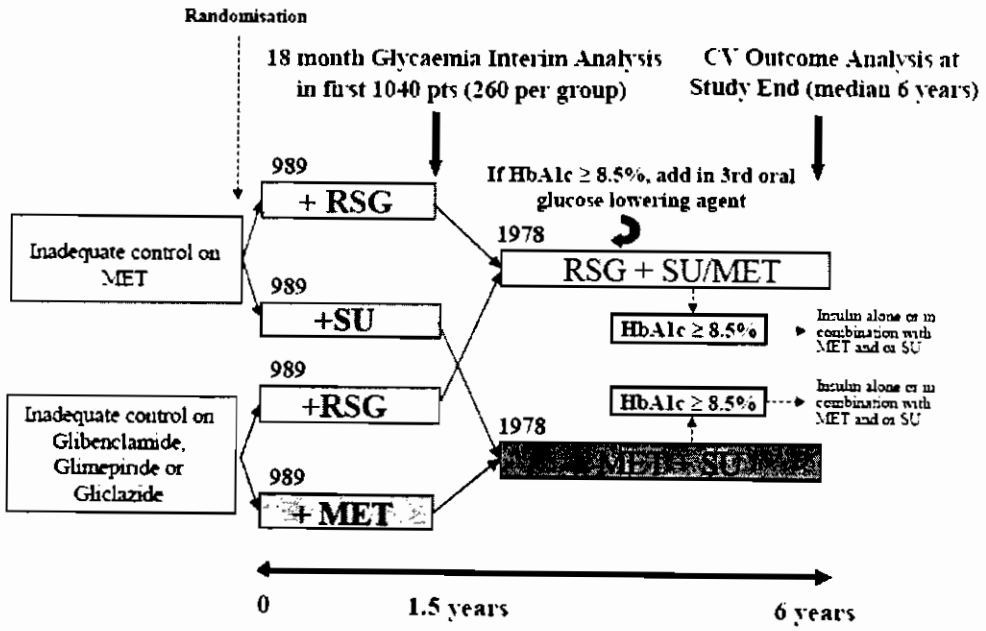
RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes)

Status: This study was initiated as a post-marketing commitment for marketing authorization by the European Medicines Agency (EMEA) in July 2000. This study was not conducted under the U.S. IND. Separate clinical/statistical reviews for RECORD by Drs. Hylton Joffe and John Lawrence are included in this briefing document. The study was initiated in April 2001, is ongoing with final results projected to be available in May 2009. However, recent publication on the increased risk of CV events and Congressional inquiries prompted release of interim study results in May 2007. The FDA has received only these interim results. No clinical datasets are available to the FDA.

Study Design:

This is a multi-center, randomized, open-label study comparing rosiglitazone in combination with either metformin or a SU to the combination of metformin and a SU in patients with type 2 diabetes. Patients on background metformin who are inadequately treated will be randomized to receive, in addition to metformin, rosiglitazone or a SU in a 1:1 ratio. Patients on background SU who are inadequately treated will be randomized to receive, in addition to the SU, rosiglitazone or metformin in a 1:1 ratio. Treatment allocation schedule was computer generated in blocks and stratified according to background treatment with either metformin or SU. Rosiglitazone was initiated at 4 mg/day. The following diagram depicts the study design.

Figure 1 Study Design



Glycemie control was targeted at HbA1c < 7.0% throughout the study with a planned interim analysis at 18 months in a subset of patients to assess glycemie control. If HbA1c is >7.0% at any point after 8 weeks of treatment, the investigator has the option to increase the dose of the *add-on* medication, but NOT the background medication. If HbA1c is ≥ 8.5% despite treatment at maximum permitted or tolerated dose of add-on medication for at least 8 weeks, a second confirmatory test is performed at least 4 weeks after the first test showing ≥ 8.5%. If this second test confirms the inadequate glycemic control

then additional therapy is initiated as depicted in the following algorithm obtained from the applicant's study protocol.

Figure 2 Treatment Algorithm for Add On Study Medication

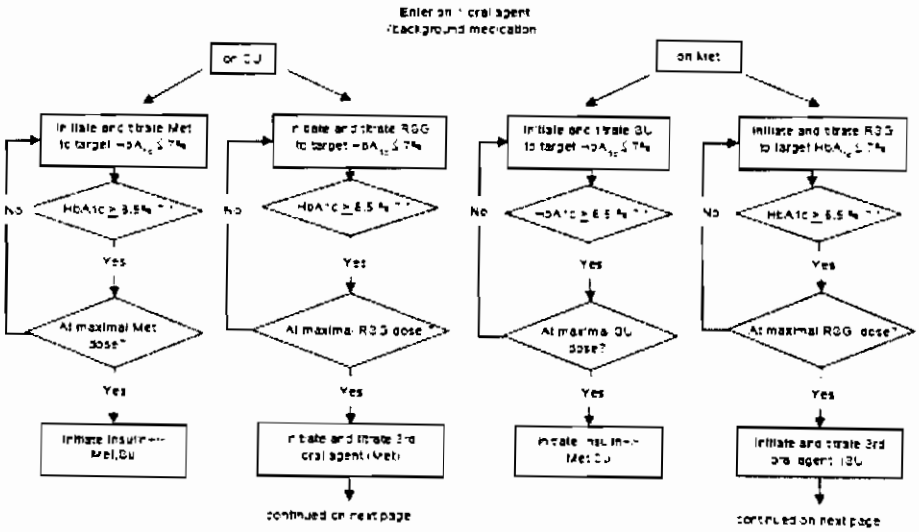
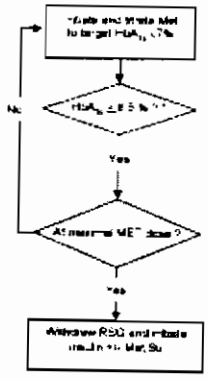


Figure 2 Treatment Algorithm for Add On Study Medication – continued



Study target : HbA1c < 7%
* Please note:
•Treatment with 3rd oral agent or insulin (= 2 oral agent) should be initiated only after two consecutive value: HbA1c ≥ 6.5% and at least 3 weeks of treatment with maximum dose of add-on study medication.

•Initiations and dose adjustments of add-on study medications and insulin should be implemented according to clinical practice and tablet strength(s) available

Background Medication - patients must be taking the following doses upon entry into the study**
- Metformin: 1.7g/day
- Glibenclamide: 15mg/day (10.5mg micronized form)
- Gliclazide: 240mg/day (90mg modified release formulation)
- Glimepiride: 4mg/day
**Patients taking lower doses (see protocol for list of exceptions) can also be eligible but they must have proven intolerance to source dose. Patients taking high doses will also be eligible.
NOTE: dose of background medication should remain unchanged throughout the study unless the patient experiences recurrent side effects. Additionally in specified circumstances, patients will be allowed to change background SU type and formulation and increase the dose of background SU or MET whilst in the RT phase of the study (see section 3.1.2.3 for details).

The dose of add-on medication (sulphonylurea or metformin) may be increased but should NOT exceed the allowable maximum dose as specified by local guidelines and labelling requirements – see section 3.1.2.3 for details).

The open-label design of this trial has been cited by some, including reviewers in FDA, as a reason for concern as it could introduce bias. Bias could include intentional or unintentional decisions regarding selection of patients for study enrollment, management of glycemia once enrolled, reporting of events, or management of ischemic events (e.g., outpatient management versus hospitalization). Notwithstanding these concerns which would have to be considered in the review of the final study results, several features of the study design may minimize such biases including:

- a central randomization process and multi-center (327 centers across 25 countries) enrollment with approximately 10-20 patients per center
- treatment algorithm for additional glycemic control
- blinded endpoint committee adjudication process

It is also important to point out in a long-term diabetes trial where titration and addition of medications is necessary, true blinding of study drug assignment may be impractical, if not impossible.

Study Objective:
The primary objective of RECORD is to compare the time to experiencing the primary combined endpoint of CV death and/or CV hospitalization between the rosiglitazone-containing treatment groups (RSG+SU/Met) and the non-rosiglitazone-containing treatment group (Met+SU). Secondary effieacy endpoints include: all cause mortality; definite heart failure; microvascular endpoints and combined CV hospitalizations or CV death endpoint plus microvascular endpoints. An independent Clinical Endpoint Committee (CEC) reviews and adjudicates all potential CV hospitalization and CV death endpoints in a blinded fashion. The CEC is comprised of at least one diabetologist, five cardiologists, and other experts as required.

All deaths are analyzed under the all-cause mortality endpoint. Deaths are further classified by the CEC as "CV" or "non-CV". CV deaths are defined as deaths for which an unequivocal non-cardiovascular cause eannot be established. CV deaths will include the following:

- death from heart failure
- death following acute MI
- sudden death
- death due to acute vascular event
- unknown deaths (cannot be categorized under the aforementioned terms) are counted as CV deaths in the primary analysis

CV hospitalizations include hospital admissions involving a change in date and include the following:

- hospitalization for acute MI
- hospitalization for definite CHF
- hospitalization for stroke
- hospitalization for unstable angina
- hospitalization for TIA
- hospitalization for invasive CV procedure or amputation of extremities due to diabetes complication (trauma-related amputations not included)
- hospitalization for other CV or undefined CV reason

This trial was designed as a non-inferiority study with the objective of showing that rosiglitazone-containing treatment is non-inferior to the non-rosiglitazone treatment if the upper limit of the 95% CI for the hazard ratio is below 1.20. A sample size of 4000 patients followed for a median of 6 years was estimated to provide 99.2% power to confirm this non-inferiority margin, given the estimated event rate was 11% per year (3% CV deaths and 8% CV hospitalizations) with an estimated 2% loss to follow-up per year.

Patient Population

This trial enrolled patients with established type 2 diabetes whose baseline HbA1c was between 7.0 and 9.0%, inclusive, and had been on a single oral glucose-lowering drug for at least 6 months prior to screening. Use of insulin or a combination of 2 or more oral agents 6 months prior to screening was an exclusion criterion. Patients were also excluded if they had been hospitalized for a major CV event in the last 3 months or had been diagnosed with heart failure. A total of 4458 patients (2228 previously on metformin and 2230 previously on SU) underwent randomization. Eleven did not receive study medication resulting in 2220 patients randomized and treated with rosiglitazone + metformin or SU versus 2227 randomized and treated with metformin + SU. The following table summarizes some baseline characteristics and demographics of the RECORD study population.

Table R1. Baseline Characteristics and Demographics of RECORD Study Cohort (from *N Engl J Med* e-publication on June 5, 2007).

Table 1. **Baseline Characteristics of the Patients.***

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)
Previous medication — no. (%)		
Metformin only	1117 (50.3)	1105 (49.6)
Sulfonylurea only	1103 (49.7)	1122 (50.4)
Age — yr	58.4±8.3	58.5±8.3
Male sex — no. (%)	1142 (51.4)	1152 (51.7)
White race — no. (%)†	2200 (99.1)	2199 (98.7)
Time since diagnosis — yr	7.0±5.0	7.1±4.9
Body-mass index	32.6±4.7	32.5±4.9
Glycated hemoglobin — %	7.9±0.7	7.9±0.7
Fasting plasma glucose — mg/dl	177±43	177±40
Hypertension — no. (%)‡	1754 (79.0)	1774 (79.7)
Ischemic heart disease — no. (%)		
Any disease	359 (16.2)	374 (16.8)
Stable angina	222 (10.0)	228 (10.2)
Myocardial infarction	102 (4.6)	114 (5.1)
Unstable angina	20 (0.9)	30 (1.3)
Cerebrovascular disease — no. (%)		
Any disease	100 (4.5)	97 (4.4)
Stroke	54 (2.4)	54 (2.4)
Transient ischemic attack	50 (2.3)	47 (2.1)
Peripheral arterial disease — no. (%)	124 (5.6)	131 (5.9)
Congestive heart failure — no. (%)	12 (0.5)	6 (0.3)
Lipid disorder — no. (%)§	2123 (95.6)	2100 (94.3)
Smoking history — no. (%)		
Current smoker	363 (16.4)	343 (15.4)
Former smoker	565 (25.5)	539 (24.2)

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was determined by the investigators.
‡ Hypertension was defined as a systolic blood pressure of more than 130 mm Hg or a diastolic blood pressure of more than 80 mm Hg.
§ A lipid disorder was defined by investigator-reported diagnosis or as a low-density lipoprotein cholesterol level of 100 mg per deciliter or more, a triglyceride level of 200 mg per deciliter or more, or a high-density lipoprotein cholesterol level of less than 40 mg per deciliter for men or less than 50 mg per deciliter for women.

Data on Baseline concomitant medications are not available to the FDA. As per Ms. Mele's review, an analysis of CV events by baseline nitrate and ACE-inhibitor use is of interest.

Ms. Mele identified two meta-groups in her analysis that had the highest OR for total ischemic events: rosiglitazone + metformin and rosiglitazone + insulin use. The use of rosiglitazone and insulin is not a pre-defined treatment group in any of the long-term studies. RECORD and perhaps BARI-2D (discussed

below) have rosiglitazone + metformin groups. In Appendix 4 (page 43) of Ms. Mele's review, a comparison of the RSG+MET meta-group to the above table shows similar baseline characteristics in these two databases. The increased ischemic risk of RSG+MET in the meta-analysis is based on a comparison to placebo+MET whereas RECORD compares RSG+MET to MET+SU. This latter comparison has more practical application in the clinical setting as patients not achieving adequate control on a single anti-diabetic regimen will require addition of other drugs. RECORD may inform prescribers which second agent should be added to failed metformin monotherapy.

Study Outcome
The study is ongoing; however, an interim analysis was performed with events collected from time of randomization until March 30, 2007. Loss to follow-up was higher and event rate was lower than predicted, raising concerns that the study will not retain enough power to meet its stated objective.

For the 4447 patients randomized and treated, mean follow-up is approximately 3.75 years. For the primary endpoints, 217 events have been adjudicated in the rosiglitazone group versus 202 in the control group yielding a HR 1.08 (95% CI: 0.89-1.31). The following interim results were submitted to the FDA and have been published in the NEJM.

Table R2: Interim Analysis from RECORD

		RSG+MET or SU N=2220	MET+SU N=2227	HR	99.9% CI 95% CI
Adjudicated or pending	**CV Death/CV hospitalization**	267 (12.0%)	243 (10.9%)	1.11	(0.83, 1.48) (0.93, 1.32)
Adjudicated	**CV Death/CV hospitalization (primary endpoint)**	217 (9.8%)	202 (9.1%)	1.08	(0.78, 1.49) (0.89, 1.31)
	Acute MI	43 (1.9%)	37 (1.7%)	1.16	(0.56, 2.43) (0.75, 1.81)
	CV Death	29 (1.3%)	35 (1.6%)	0.83	(0.36, 1.9) (0.51, 1.36)
	CV Death/Stroke/MI[1]	93 (4.2%)	96 (4.3%)	0.97	(0.60, 1.56) 0.73, 1.29)
	Stroke	29 (1.3%)	38 (1.7%)	0.76	(0.34, 1.71) (0.47, 1.23)
	Heart Failure	38 (1.7%)	17 (0.8%)	2.24	(0.86, 5.85) (1.27, 3.97)
	CV Death/Stroke/MI/UA	109 (4.9%)	110 (4.9%)	0.99	(0.64, 1.55) (0.76, 1.29)
Adjudication not required	**All-cause mortality**	74 (3.3%)	80 (3.6%)	0.925	(0.54, 1.57) (0.67, 1.27)

1 MACE or APTC composite

Notwithstanding that these are interim results and the study was designed as a non-inferiority study with an upper bound of the 95% CI of 1.2, these results show no conclusive evidence that rosiglitazone has a statistically significant increase risk for ischemic events compared to metformin or sulfonylurea. It is reassuring, given the findings of the meta-analysis of shorter term trials, that the point estimate of the upper bounds of the 95% CI for the combined CV death/MI/Stroke excludes HR higher than 1.3.

BARI-2D (The Bypass Angioplasty Revascularization Investigation 2 Diabetes)
Status: This study is sponsored by the National Institutes of Health (NIH), National Heart Lung and Blood Institute (NHLBI) and is currently ongoing. It is not conducted under the IND for Avandia® and the FDA does not have any clinical datasets for review. Dr. David Gordon from the NHLBI has been invited to present the study design and objectives for purposes of providing the committee members of knowledge on future cardiovascular data that may potentially address rosiglitazone CV safety concerns.

Study Design and Study Objectives: This is a 2x2 factorial design trial comparing revascularization combined with aggressive medical management of T2DM versus aggressive medical management alone in patients with documented stable CAD. In addition, the factorial design seeks to compare 2 glycemic treatment strategies: insulin-sensitizing versus insulin-providing therapies. The following two hypotheses are tested in this trial:

1. Coronary revascularization hypothesis: a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive medical therapy alone.

2. Method of glycemic control hypothesis: with a target of HbA1c < 7.0%, a strategy of hyperglycemia management directed at insulin sensitization results in lower 5-year mortality compared to a strategy of insulin provision.

Insulin sensitizing drugs included metformin and TZDs. As per correspondence between Dr. Nesto (one of the PIs) and the applicant, the agency was informed that approximately 90% of the TZD used is rosiglitazone. Insulin providing drugs include SU, glinides, and insulin. A detailed glycemic control strategy is established for each treatment group to ensure uniform levels of HbA1c. In addition, other risk factors for CHD such as hypertension, dyslipidemia, tobacco use, and obesity are intensively monitored and managed by separate committees to ensure uniformity of results and in compliance with current treatment guidelines.

A total of 2800 patients was targeted to be randomized to initial elective revascularization with aggressive medical therapy or aggressive medical therapy alone with equal probability, and simultaneously being assigned at random to an insulin-providing or insulin-sensitizing glycemic control regimen as summarized from the Manual of Operations for this trial.

Number of Patients Per Treatment Assignment		Revascularization Strategy	
		Revascularization	Medical
Glycemic Control Strategy	Insulin Providing (IP)	700	700
	Insulin Sensitizing (IS)	700	700

The primary endpoint is all-cause mortality.
The principal secondary endpoint is the composite of death, MI, or stroke.
Other secondary endpoints are discussed in the publications provided under Appendix 7.

At the time of the publication of the trial design in *American Journal of Cardiology* June 2006, 2368 patients had been enrolled at 49 clinical centers.

Patient Population
Unlike other studies described in this memo thus far, this trial specifically targets patients with established heart disease. The inclusion and exclusion criteria are summarized below:

Inclusion Criteria for BARI 2D
1. Diagnosis of Type 2 diabetes mellitus.
2. Coronary arteriogram showing one or more vessels amenable to revascularization (≥50% stenosis).
3. Objective documentation of ischemia OR subjectively documented typical angina with ≥70% stenosis in at least one artery.
4. Suitability for coronary revascularization by at least one of the available methods (does not require the ability to achieve complete revascularization).
5. Ability to perform all tasks related to glycemic control and risk factor management.
6 Age 25 or older.
7. Informed written consent.

Exclusion Criteria for BARI 2D
1. Definite need for invasive intervention as determined by the attending cardiologist.
2. Prior bypass surgery (CABG) or prior catheter-based intervention within the past 12 months.
3. Planned intervention for disease in bypass graft(s) if the patient is randomized to a strategy of initial revascularization.
4. Class III or IV CHF.
5. Creatinine ≥ 2.0 mg/dl.
6. HbA1c ≥ 13%.
7. Need for major vascular surgery concomitant with revascularization (*e.g.*, carotid endarterectomy).
8. Left main stenosis ≥ 50%.
9. Non-cardiac illness expected to limit survival.
10. Hepatic disease (ALT > 2 times the ULN).
11. Fasting triglycerides ≥ 1000 mg/dl in the presence of moderate glycemic control (HbA1c ≤ 9.0%).
12. Current alcohol abuse.
13. Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg. of Prednisone per day or the equivalent.
14. Pregnancy, known, suspected, or planned in next 5 years.
15. Geographically inaccessible or unable to return for follow-up.
16. Enrolled in a competing randomized trial or clinical study.
17. Unable to understand or cooperate with protocol requirements

With respect to the meta-analysis, the BARI-2D population may be most similar to Studies 211 and 352 summarized in Appendix 4 of Ms. Mele's review. These were the only studies in the meta-analysis which specifically enrolled patients with a history of heart disease (Study 352) or Class I or II heart failure (Study 211).

Study Outcomes: No interim data have been provided to the FDA. The Agency was informed that the DSMB was previously aware of the GSK meta-analysis results. Shortly after the publication of Dr. Nissen's meta-analysis, the DSMB re-convened an unplanned meeting and after a review of the available data, a decision was again made to continue with the trial without modification.

PIOGLITAZONE

PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events)
PROactive is the only completed prospective CV outcomes trial with a TZD. This was a European trial involving 321 study centers, and had a randomized, double-blind, placebo-controlled, parallel group design. A total of 5,238 patients participated, with 2,605 in the pioglitazone treatment group, and 2,633 in the placebo group. Patients were men and women with type 2 diabetes who had a hemoglobin A1c value at entry of >6.5%. Ages ranged from 35-75 years. All patients had a history of macrovascular disease, which was predefined. Notable exclusion criteria include heart failure at entry (NYHA FC 2 or higher), recent insulin monotherapy, or the current use of any TZD. The mean duration of treatment was 34.5 months.

The following tables summarizes certain relevant Baseline characteristics of the PROactive cohort.

Table P1: Mean Baseline Characteristics in PROactive

Characteristic	Pioglitazone N=2605 Mean (SD)	Placebo N=2633 Mean (SD)	Overall N=5238 Mean (SD)
Age (yrs)	61.9 (7.6)	61.6 (7.8)	61.8 (7.7)
Duration of diabetes (yrs)	9.4 (6.9)	9.6 (7.1)	9.5 (7.0)
Weight (kg)	87.6 (15.5)	88.5 (15.6)	88.0 (15.6)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Body mass index (BMI) (kg/m^2)	30.7 (4.7)	31.0 (4.8)	30.9 (4.8)
Waist circumference[1] (cm)	104.9 (11.7)	105.5 (12.1)	105.2 (11.9)
Systolic blood pressure (mm Hg)	143.5 (17.7)	143.3 (17.8)	143.4 (17.8)
Diastolic blood pressure (mm Hg)	82.8 (9.9)	83.2 (9.4)	83.0 (9.7)

Source: Applicant's Table 10.c, pg 68, Part A, study report
1 Waist circumference measured at the midpoint between the lower rib margin and the iliac crest

Table P2: Summary of Macrovascular Disease Entry Criteria in PROactive

Characteristic	Pioglitazone N=2605 n (%)	Placebo N=2633 n (%)	Overall N=5238 n (%)
MI at least 6 months before entry into study	1230 (47.2)	1215 (46.1)	2445 (46.7)
Stroke at least 6 months before entry into study	486 (18.7)	498 (18.9)	984 (18.8)
PCI or CABG at least 6 months before entry into study	804 (30.9)	807 (30.6)	1611 (30.8)
ACS at least 3 months before entry into study	355 (13.6)	360 (13.7)	715 (13.7)
Objective evidence of coronary artery disease	1246 (47.8)	1274 (48.4)	2520 (48.1)
Symptomatic peripheral arterial obstructive disease	504 (19.3)	539 (20.5)	1043 (19.9)
≥ 2 criteria	1223 (46.9)	1278 (48.5)	2501 (47.7)

Source: Applicant's Table 10.d, pg 69, Part A, study report

Table P3: Baseline Mean and Median HbA1c, Lipid and Creatinine Values in PROactive

Parameter	Pioglitazone N = 2605		Placebo N = 2633	
	Mean (SD)	Median (IQR[1])	Mean (SD)	Median (IQR)
HbA1c (%)	8.1 (1.4)	7.8 (7.0-8.9)	8.1 (1.4)	7.9 (7.1-8.9)
LDL (mg/dL)	114.5 (36.0)	111.8 (88.9-135.3)	114.5 (36.9)	110.6 (88.9-135.3)
HDL (mg/dL)	44.9 (12.3)	42.5 (34.8-50.3)	44.9 (11.8)	42.9 (34.8-50.3)
TG (mg/dL)	197.5 (163.6)	160.3 (115.1-230.3)	199.3 (158.0)	162.1 (115.1-230.3)
Cr (mg/dL)	0.9 (0.2)	0.9 (0.8-1.0)	0.9 (0.3)	0.9 (0.8-1.1)

1 Interquartile range
Source: Applicant's Table 10.e., pg 70, Part A, study report

Table P4: Baseline Antidiabetes Therapy in PROactive

Therapy	Pioglitazone N = 2605 n (%)	Placebo N = 2633 n (%)
Metformin only	253 (9.7)	261 (9.9)
Sulfonylureas only	508 (19.5)	493 (18.7)
Metformin + sulfonylureas only	654 (25.1)	660 (25.1)
Insulin only	5 (0.2)	8 (0.3)
Insulin + metformin	456 (17.5)	475 (18.0)
Insulin + sulfonylureas	209 (8.0)	219 (8.3)
Insulin + metformin + sulfonylureas	105 (4.0)	107 (4.1)
Other	306 (11.7)	305 (11.6)
Diet only	109 (4.2)	105 (4.0)

Source: Applicant's Table 10.f., pg 71, Part A, study report

Table P5 Baseline Cardiovascular Medications in PROactive

Medications	Pioglitazone N = 2605 n (%)	Placebo N = 2633 n (%)
Antiplatelet medications	2221 (85.3)	2175 (82.6)
Angiotensin converting enzyme (ACE) inhibitors	1630 (62.6)	1658 (63.0)
Beta blockers	1423 (54.6)	1434 (54.5)
Statins	1108 (42.5)	1137 (43.2)
Nitrates	1018 (39.1)	1137 (39.7)
Calcium channel blockers	892 (34.2)	964 (36.6)
Thiazide diuretics	401 (15.4)	430 (16.3)
Loop diuretics	372 (14.3)	378 (14.4)
Fibrates	264 (10.1)	294 (11.2)
Angiotensin II receptor antagonists	170 (6.5)	184 (7.0)
Alpha blockers	155 (6.0)	154 (5.8)
Potassium sparing diuretics	159 (6.1)	178 (6.8)
Cardiac glycosides	129 (5.0)	127 (4.8)

Source: Applicant's Table 10.g, pg 71, Part A, study report

Study treatments were added to the patients' entry diabetes medications. Patients were randomized to the addition of pioglitazone or a matching placebo. Pioglitazone was initiated at 15 mg/day and was force-titrated to 45 mg/day over a period of two months. Titration was permitted for underlying medications for diabetes, hypertension and lipids; International Diabetes Federation goals were to be used to guide titration. Despite these recommendations, there were imbalances between the two treatment groups for

control of certain risk factors for CVD, generally favoring the pioglitazone treatment group. Consequently, it is difficult to determine if any favorable CV observations are due to a positive effect of pioglitazone or these imbalances in CV risk factors. Recall that one of the BARI-2D objectives is to achieve uniform control of multiple CV risks to avoid imbalance that complicate the interpretation of final study results.

The following table summarizes HbA1c change in PROactive over the study duration. Other imbalances between pioglitazone and placebo groups, respectively, include a 12.1% versus 8.4% increase in HDL-C and a 4.0 mmHg versus 2.6 mmHg reduction in systolic BP at final visit.

Table P6: Mean Change from Baseline in HbA1c (%) in PROactive

	Pioglitazone		Placebo	
Visit	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	2568	8.1 (1.4)	2597	8.1 (1.4)
6 months	2414	-0.8 (1.2)	2405	-0.1 (1.2)
12 months	2368	-0.9 (1.2)	2386	-0.3 (1.2)
24 months	2256	-0.8 (1.3)	2236	-0.2 (1.3)
Final visit	2249	-0.9 (1.3)	2258	-0.4 (1.4)

Source: Applicant's Table 11.r., pg 93, Part A, study report

The primary efficacy endpoint, measured at end-of-study, was a composite of:

- All-cause mortality
- Nonfatal myocardial infarction (including silent MI)
- Stroke
- Acute coronary syndrome
- Cardiac intervention (coronary artery bypass grafting or percutaneous coronary intervention)
- Major leg amputation (above ankle)
- Bypass surgery or revascularization in the leg

Neither the primary endpoint, nor any of the other efficacy endpoints, included heart failure.

The difference between pioglitazone and placebo for the primary endpoint was not statistically significant. Patients in the pioglitazone group experienced 514 first events (19.7% of patients), compared to 572 first events in the placebo group (21.7% of patients), for a hazard ratio of 0.90 (95% confidence interval [CI] 0.80, 1.02; p 0.0954). This was measured at end-of-study for each patient, with a mean follow-up of 34.5 months. There was no significant interaction by baseline diabetes therapy or ACE-inhibitor use. On June 19, 2007, a request was made to Takeda to analyze the primary endpoint and its components by baseline nitrate use. The response to this request is pending.

The statistical plan left no alpha for consideration of secondary endpoints in the event of a failed primary. Therefore, all secondary endpoints would be considered exploratory. Predefined secondary endpoints included cardiovascular mortality, and the individual components of the primary endpoint. There was no significant difference between pioglitazone and placebo for any of these individual endpoints; point estimates for most hazard ratios were <1, favoring pioglitazone, but all 95% confidence intervals (CIs) included one.

Table P7: Results for Predefined Secondary Endpoints for PROactive (Measured at End-of-Study, Mean Follow-up 34.5 Months)

Endpoint	Pio N=2605 n (%)	Pbo N=2633 n (%)	HR (95% CI)	p-value
Cardiovascular mortality	127 (4.9)	136 (5.2)	0.94 (0.74, 1.20)	0.6163
All-cause mortality	177 (6.8)	186 (7.1)	0.96 (0.78, 1.18)	0.6784
Nonfatal myocardial infarction	119 (4.6)	144 (5.5)	0.83 (0.65, 1.06)	0.1312
Stroke	86 (3.3)	107 (4.1)	0.81 (0.61, 1.07)	0.1398
Acute coronary syndrome	56 (2.1)	72 (2.7)	0.78 (0.55, 1.11)	0.1680
Major leg amputation	26 (1.0)	26 (1.0)	1.01 (0.58, 1.73)	0.9822
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	169 (6.5)	193 (7.3)	0.88 (0.72, 1.08)	0.2335
Leg revascularization	80 (3.1)	65 (2.5)	1.25 (0.90, 1.73)	0.1884

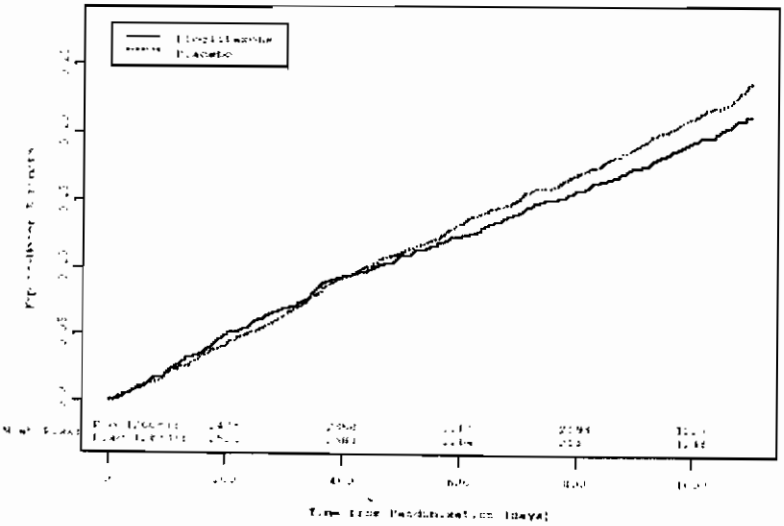
Source: Takeda's Tables 11.a., 11.g., and 11.h.; pgs 74, 80 and 81; part A, PROactive study report

PROactive ended on 31 Jan 05. On 12 May 05, Takeda submitted a new statistical plan with a new endpoint, which they designated their "main secondary endpoint". Takeda stated that unblinding occurred on 23 May 05. Because of the chronology of the addition of this endpoint, and because it was added in a trial with a failed primary endpoint, this endpoint appeared to be more consistent with an exploratory post hoc analysis rather than a prospectively defined endpoint. For this endpoint, which included all-cause mortality, nonfatal myocardial infarction (excluding silent myocardial infarction), and stroke, measured at end of follow-up, Takeda reported a statistically significant difference between pioglitazone and placebo, favoring pioglitazone. In the pioglitazone group, a total of 301 first events occurred (11.6% of patients), while there were 358 first events in the placebo group (13.6% of patients). This was associated with a hazard ratio of 0.84 (95% CI 0.72, 0.98; p 0.0277, without adjustment for multiple comparisons). Because of the potential bias associated with selection of individual components in a post hoc fashion, this endpoint raises concerns for the selection of a "best case scenario" endpoint.

The long-term nature of PROactive was important; if it had been a study of 6 months or less (as were 38/42 studies in the rosiglitazone retrospective pooled studies analyses), point estimates would have favored placebo rather than pioglitazone for the primary endpoint and most of its individual components (including myocardial infarction), as illustrated in the following table and Kaplan-Meier plots.

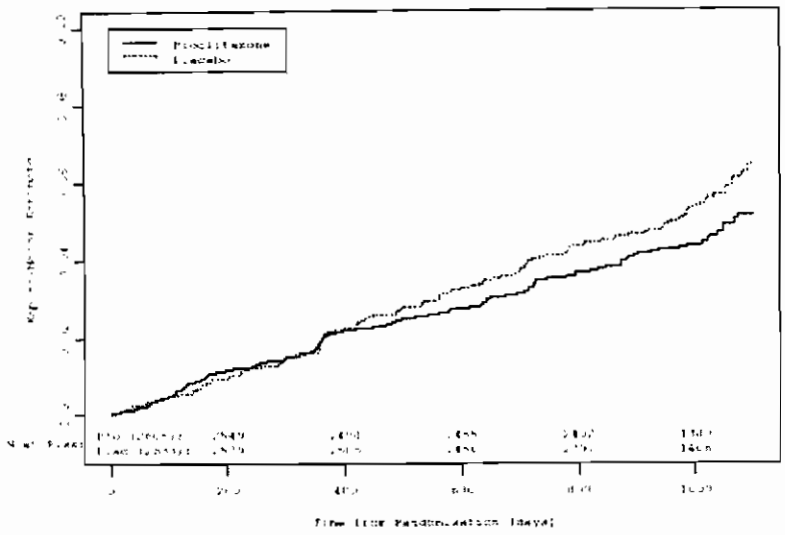
Table P8: Results for Predcfined Secondary Endpoints for PROactive (Measured at 6 Months)			
Endpoint	**Pio N=2605 n (%)**	**Pbo N=2633 n (%)**	**HR[1]**
Cardiovascular mortality	20 (0.8)	27 (1.0)	0.8
All-cause mortality	25 (1.0)	30 (1.1)	0.9
Nonfatat myocardial infarction	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3
Acute coronary syndrome	14 (0.5)	8 (0.3)	1.7
Major leg amputation	4 (0.2)	2 (0.1)	2.0
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	33 (1.3)	32 (1.2)	1.1
Leg revascularization	18 (0.7)	9 (0.3)	2.3
Source: Tables 1-12, Table 2.1, Table 2.2, provided by Takeda by email 13 May 07 **1 Pio rate/ pbo rate; confidence intervals for the 6-month hazard ratios not provided**			

Figure P1: Kaplan-Meier Plot of Time to Primary Composite Endpoint, PROactive Trial of Pioglitazone



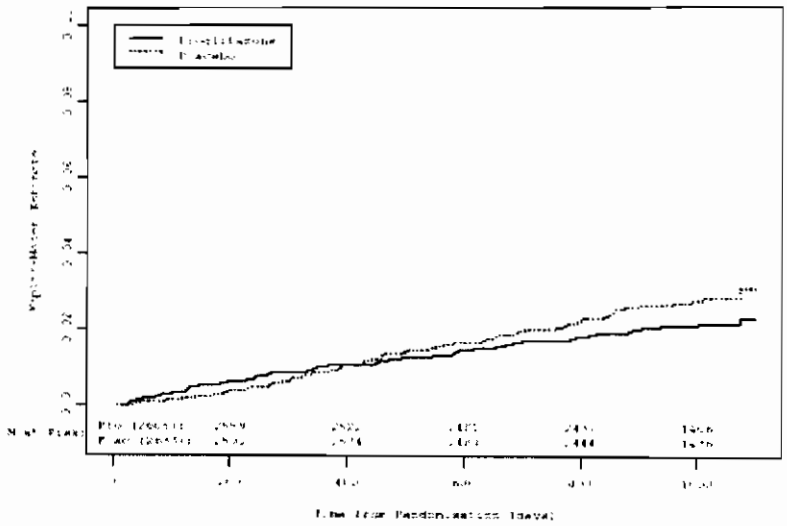
Source: Figure 15.2.1, pg 388, PROactive study report, NDA 21073 supplement 026

Figure P2: Kaplan-Meier Plot of Time to Nonfatal Myocardial Infarction, PROactive Trial of Pioglitazone



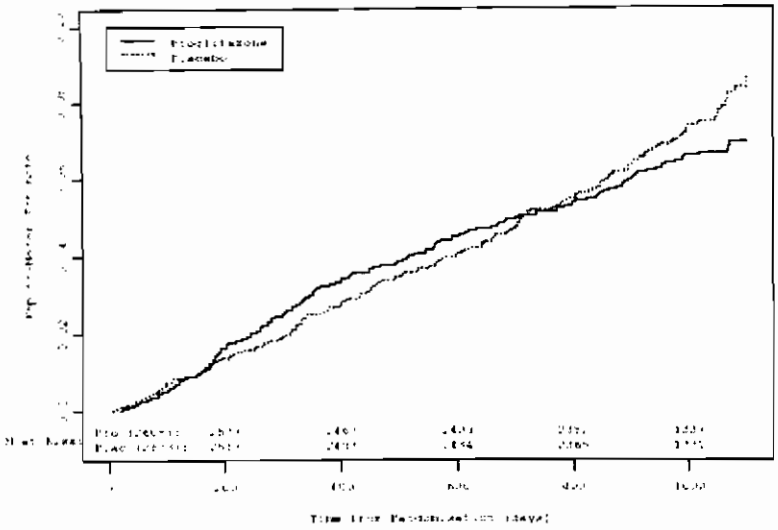
Source: Figure 15.2.4.2, pg 394, PROactive study report, NDA 21073 supplement 026

Figure P3: Kaplan-Meier Plot of Time to Acute Coronary Syndrome, PROactive Trial of Pioglitazone



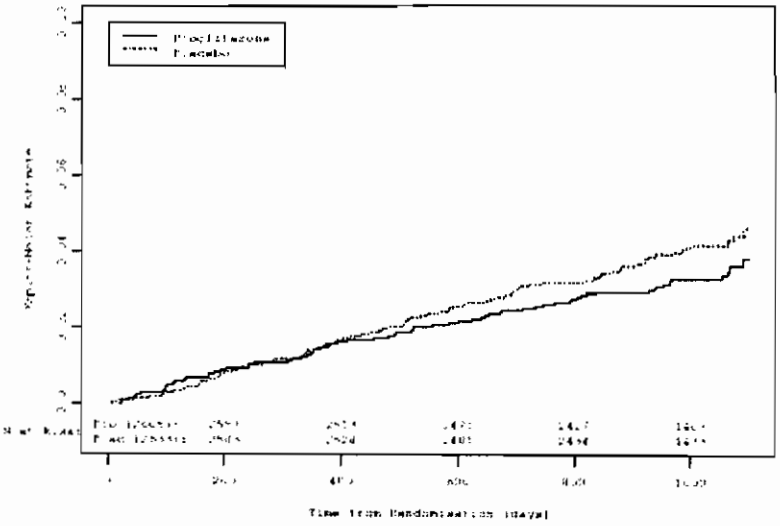
Source: Figure 15.2.4.3, pg 395, PROactive study report, NDA 21073 supplement 026

Figure P4: Kaplan-Meier Plot of Time to Cardiac Intervention (Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention), PROactive Trial of Pioglitazone



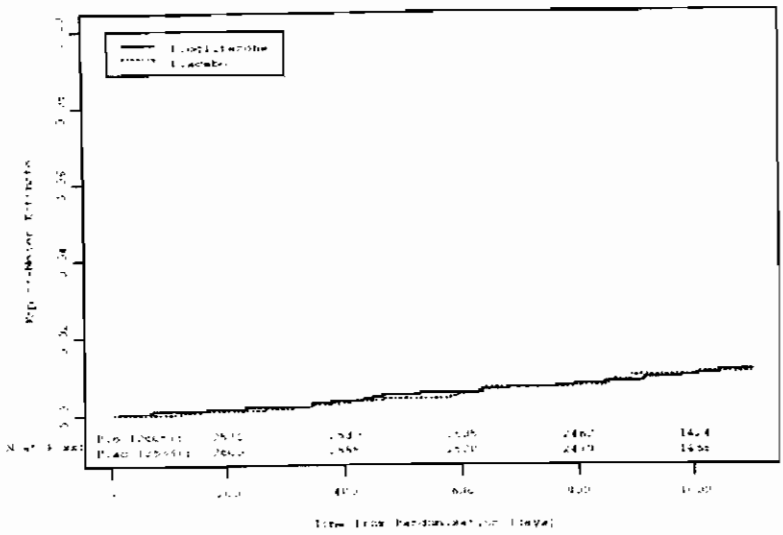
Source: Figure 15.2.4.4, pg 396, PROactive study report, NDA 21073 supplement 026

Figure P5: Kaplan-Meier Plot of Time to Stroke, PROactive Trial of Pioglitazone



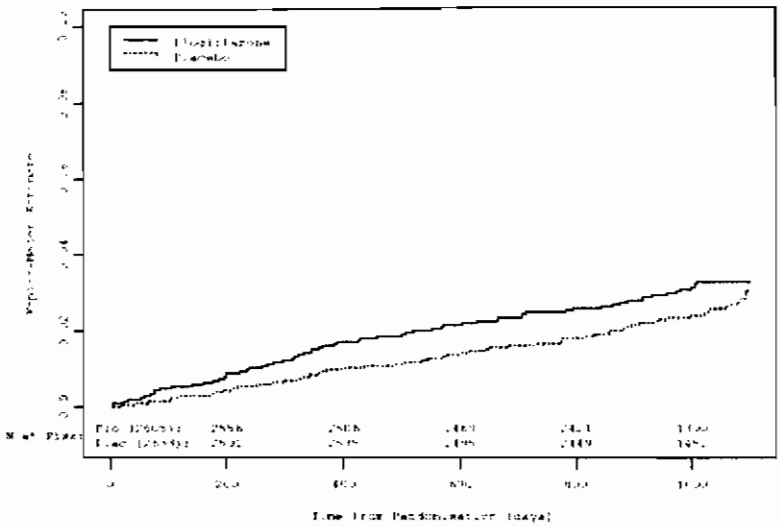
Source: Figure 15.2.4.5, pg 397, PROactive study report, NDA 21073 supplement 026

Figure P6: Kaplan-Meier Plot of Time to Major Leg Amputation, PROactive Trial of Pioglitazone



Source: Figure 15.2.4.6, pg 398, PROactive study report, NDA 21073 supplement 026

Figure P7: Kaplan-Meier Plot of Time to Bypass Surgery or Revascularization in the Leg, PROactive Trial of Pioglitazone



Source: Figure 15.2.4.7, pg 399, PROactive study report, NDA 21073 supplement 026

Had PROactive been a six-month study, one might have been concerned about a possible increased macrovascular risk with pioglitazone. In the longer term, pioglitazone had a neutral effect on macrovascular outcomes, which were associated with favorable hazard ratios. Separation of curves on Kaplan-Meier plots did not become favorable for pioglitazone until after 400 days of study for the primary endpoint, and for secondary endpoints of myocardial infarction, acute coronary syndrome and stroke. There are limits to the interpretation of these six-month data, including confounding introduced by the censoring of data from patients who died, and relatively low event rates at that 6-month point. Nevertheless, presentation of these 6-month data illustrate that clinically meaningful analyses of

cardiovascular outcomes typically require long-term follow-up and accumulation of a minimum number of events.

There are no clear data demonstrating the long-term reduction of risk of macrovascular events for any diabetes drug. In the Diabetes Control and Complications Trial (DCCT 1998, 1993), aggressive control of HbA1c in type 1 diabetic patients with intensive insulin therapy was associated with a reduced risk of microvascular events, such as diabetic retinopathy. In the DCCT, there was an initial worsening of retinopathy, followed by long-term reduction in progression, for intensive-control group patients compared to "conventional-control" group patients. This microvascular benefit of HbA1c-lowering took time to declare itself.

As mentioned earlier, Takeda did not include heart failure in any of the PROactive endpoints. The incidence of serious heart failure among patients in the pioglitazone group was 5.7%, compared to 4.1% in the placebo group. If one were to add these events to any of the efficacy composites, the difference between pioglitazone and placebo for overall cardiovascular risk would be negligible.

While the Division of Metabolism and Endocrinology Products (DMEP) did not consider the efficacy findings of the trial significant enough to permit Takeda to promote pioglitazone as having a cardiovascular benefit, DMEP did feel that the neutrality of the trial for long-term risk of macrovascular events other than heart failure was important safety information. Therefore, although Takeda requested the addition of efficacy information, including their post hoc secondary endpoint, to the Clinical Studies section of the Actos® label, DMEP did not concur. However, in order to convey what DMEP felt was a significant safety finding, a table of the results for the components of the primary composite endpoint was included in the Adverse Reactions section. The heart failure findings in PROactive were important, and were included in the Warnings section.

Study H6E-US-GLAI Study of Lipid Effects of Pioglitazone vs Rosiglitazone
This was a 6-month, double-blind trial involving 369 patients randomized to pioglitazone 30 mg daily for 12 weeks followed by 45 mg daily for 12 weeks, and 366 patients randomized to rosiglitazone 4 mg once daily for 12 weeks followed by 4 mg twice daily for 12 weeks. The primary endpoint was change in triglyceride level. This study was submitted as a supplement to the NDA for pioglitazone requesting comparative lipid-efficacy claims in January 2005. The application was not approved as the clinical relevance of greater TG-lowering associated with pioglitazone over rosiglitazone was not known. The following table summarizes the lipid changes at Week 24 for the two treatment groups.

	Actos	Avandia
TG (% change from baseline)	-12	15
HDL-C (% change)	15	8
LDL-C (% change)	16	23
Total-C (% change)	6	16

The difference in lipid effects between these two drugs was already known as these two agents were approved in 1999 and their applications were discussed within days of each other at a public advisory committee with the unfavorable lipid effects of rosiglitazone also included in its approved labeling.

This study was not designed as a cardiac safety study and cardiac serious adverse events were not adjudicated. There was one death in the pioglitazone group (MVA) and two in the rosiglitazone group (brain tumor and found deceased in hotel room). There were two cardiac serious adverse events in the pioglitazone group (0.3%) and 6 (1.6%) in the rosiglitazone group. Pioglitazone group cardiac SAEs

included one event each of myocardial infarction and triple-vessel CABG. Rosiglitazone group cardiac SAEs included one event each of myocardial infarction, triple-vessel CABG, unstable angina, coronary artery occlusion, coronary artery atherosclerosis and "chest pain cardiac".

Meta-analysis of Pioglitazone Controlled Clinical Trials
On April 23, 2007, the agency requested that Takeda perform a similar meta-analysis to that performed for rosiglitazone. Studies to consider included double-blind, randomized, placebo/comparator controlled trials of at least 12 weeks' duration. The company was asked to submit a statistical plan for a formal meta-analysis of MI and CHF.

On June 1, 2007, the agency received a tabular summary of pioglitazone clinical safety and efficacy studies. Review of the pioglitazone studies which meet the criteria for inclusion in a meta-analysis revealed notable differences between the rosiglitazone and pioglitazone clinical trials.

- In the rosiglitazone database, about **85%** of the database is placebo-controlled while in pioglitazone only approximately **18%** are against placebo
- In the rosiglitazone database, about **15%** of the database is head to head against SU while in pioglitazone about **63%** is against SU
- In the rosiglitazone database, about **23%** of the database is add-on to metformin/placebo controlled while in the pioglitazone database the number is only **6%**
- In the rosiglitazone database, about **26%** of the patients were naïve to therapy while in the pioglitazone database the number is about **48%**

As noted in Ms. Mele's review of the rosiglitazone meta-analysis, overall comparisons of rosiglitazone to placebo showed an increased risk (OR ~ 1.5) while comparisons head-to-head against metformin or SU did not demonstrate an increased risk (OR ~ 0.8). A greater risk was also observed in previously-treated patients versus patients naïve to therapy. These differences raise concern on the comparability of meta-analyses of the two TZDs.

At the time of preparation of this document, the statistical plan has not been received by the Agency. Given the time constraints and reviewer resources, it is unlikely a meaningful meta-analysis of pioglitazone controlled studies will be performed by the July 30th advisory committee meeting date.

Analysis of a Common Cardiovascular Endpoint Composite Across Data Sources

The data sources which have been discussed in this briefing document are heterogeneous, and a variety of endpoints have been used to assess cardiovascular safety. In the meta-analysis of pooled short-term diabetes studies, the major endpoints used to assess myocardial ischemic event risk were retrospectively-defined groupings of a large number of adverse event terms. In DREAM, RECORD, and PROactive, there are predefined and adjudicated composite and individual endpoints, but the exact composites differ from study to study. Biometricians and clinicians, both within and outside of the FDA, have suggested that use of a common composite endpoint could allow for a better perspective on the risk information provided by these data sources. There are many endpoints which could be considered. In large cardiovascular outcome trials, composite endpoints are often used which contain individual endpoints which are felt to be important serious events for which there is a relatively good likelihood that the assigned event term actually represents the event in question. One endpoint that is commonly used in cardiovascular outcome trials is a composite of cardiovascular death, myocardial infarction and stroke, sometimes referred to as the MACE (Major Adverse Cardiovascular Events) endpoint. After discussions with the FDA regarding the desirability of utilizing a common endpoint across data sources, GSK performed analyses utilizing a composite of cardiovascular death, serious adverse events of myocardial infaretion, and serious adverse events of stroke. FDA Biometricians also performed analyses of this composite endpoint. These analyses have significant limitations: some events were adjudicated and

some were not; inclusiveness of terms included in the composite is difficult to confirm and compare; and the heterogeneity of the study populations limits comparability. However, there may be some value in assessing whether the estimates for cardiovascular risk generally trend in the same direction across data sources.

The following table presents this "MACE" composite for the major data sources presented in this document. The table is followed by a description of some of the limitations of these analyses. They should not be interpreted as a "final answer" about the cardiovascular risk assoeiated with rosiglitazone.

Table M1: Analyses of a Composite of Cardiovascular Death, Myocardial Infarction and Stroke ("MACE"), and Its Components, for the Rosiglitazone Pooled Studies Meta-Analysis, and for the Large Longterm Clinical Trials of Thiazolidinediones

			HR or OR (95% CI), p-value			
Data Source	**Comparison**	**Analysis Model**	**CV Mort + MI + Stroke ("MACE")**	**CV Mort**	**MI**	**Stroke**
Meta-analyses of pooled diabetes treatment studies[1]	**ALL RSG vs ALL CONTROL**	**GSK model**	HR 1.161 (0.773, 1.744), p=0.4731	HR 1.914 (0.790, 4.635), p=0.1502	HR 1.590 (0.934, 2.706), p=0.0875	HR 0.475 (0.231, 0.976), p=0.0428
		FDA exact model (excludes studies with zero events in both arms)	OR 1.2 (0.8, 1.8), p=0.4	OR 1.7 (0.7, 5), p=0.2	OR 1.5 (0.9, 2.7), p=0.11	OR 0.6 (0.2, 1.2), p=0.10
		FDA MH model (no studies excluded)	OR 1.15 (0.8, 1.6), p>0.3			
ADOPT[2]	**RSG vs SU**	**GSK model**	HR 1.188 (0.739, 1.908), p=0.4771	HR 0.582 (0.190, 1.783), p=0.3429	HR 1.518 (0.785, 2.938), 0.2149	HR 0.944 (0.430, 2.071), p=0.8849
		FDA Model	HR 1.2 (0.7, 1.9), p=0.3	HR 0.6 (0.2, 1.9), p=0.4	HR 1.6 (0.8, 3.1), p=0.17	HR 0.9 (0.4, 2.1), p=0.9
	RSG vs MET	**GSK model**	HR 1.109 (0.709, 1.735), p=0.6500	HR 1.304 (0.350, 4.859), p=0.6929	HR 1.227 (0.677, 2.221), p=0.5004	HR 0.773 (0.376, 1.593), p=0.4860
		FDA model	HR 1.1 (0.7, 1.8), p=0.6	HR 1.3 (0.4, 5), p=0.7	HR 1.3 (0.7, 2.3), p=0.4	HR 0.8 (0.4, 1.6), p=0.5

Table M1: Analyses of a Composite of Cardiovascular Death, Myocardial Infarction and Stroke ("MACE"), and Its Components, for the Rosiglitazone Pooled Studies Meta-Analysis, and for the Large Longterm Clinical Trials of Thiazolidinediones

			HR or OR (95% CI), p-value			
Data Source	Comparison	Analysis Model	CV Mort + MI + Stroke ("MACE")	CV Mort	MI	Stroke
DREAM[3]	ALL RSG vs ALL CONTROL (RSG group + RSG+RAM group vs PBO group + RAM group)	DREAM investigators model	HR 1.39 (0.81, 2.37), p=0.2	HR 1.20 (0.52, 2.77), p=0.7	HR 1.66 (0.73, 3.80), p=0.2	HR 1.39 (0.44, 4.40), p=0.6
		FDA model	OR 1.44 (0.82, 2.58), p= 0.23	OR 1.20 (0.47, 3.11), p=0.83	OR 1.78 (0.74, 4.58), p=0.23	OR 1.40 (0.38, 5.60), p=0.77
	RSG group vs PBO group	FDA model	OR 1.07 (0.48, 2.4), P=1	OR 1.00 (0.23, 4.34), p=1	OR 0.83 (0.20, 3.27), p=0.77	OR 1.66 (0.32, 10.7), p=0.73
	RSG+RAM group vs RAM group	FDA model	OR 2.02 (0.86, 5.12), p=0.09	OR 1.41 (0.38, 5.63), p=0.58	OR 3.70 (0.97, 20.7), p=0.03	OR 1.00 (0.07, 13.8), p=1
RECORD interim analysis[4]	ALL RSG vs ALL CONTROL	GSK with only adjudicated events	HR 0.97 (0.73, 1.29), p=0.83	HR 0.83 (0.51, 1.36), p=0.46	HR 1.16 (0.75, 1.81), p=0.50	component analysis not published
		GSK with all events (adjudicated and nonadjudicated)	HR 0.96 (0.74, 1.24), p=0.74	HR 0.80 (0.52, 1.24), p=0.32	HR 1.23 (0.81, 1.86), p=0.34	component analysis not published
PROactive[5]	ADD-ON PIO vs ADD-ON PBO	Takeda model	HR 0.82 (0.70, 0.97), p=0.0201	HR 0.94 (0.74, 1.20), p=0.6163	component analysis not provided	HR 0.81 (0.61, 1.07), p=0.1398

1 N.B. Heterogeneity across the pooled studies reduces the reliability of an overall estimate. See Ms. Mele's statistical review of 3 Jul 07 for details on these analyses by meta-group.
GSK analyses used proportional hazards model including covariate for baseline risk and term for treatment. Included CV mortality, MI SAEs and stroke SAEs. NDA 21071 sub 31 May 07, pg 5
FDA analyses by J Mele: FDA "exact model" = exact test with conditional maximum likelihood estimates where studies with zeros in both arms are excluded; stratified by meta-groups. FDA "MH" model = Mantel-Haenszel fixed effects model with continuity correction where no trials are excluded. MI = MI SAEs, stroke = stroke SAEs.
2 GSK analyses source NDA 21071 EDR 31 May 07, proportional hazards model with terms for treatment and number of major CV risk factors
FDA analyses by J Mele, DFS 3 Jul 07; proportional hazards model with terms for treatment and number of major CV risk factors, and with gender as stratifier
3 DREAM investigators model (DREAM Investigators, 2006), analyses with Cox proportional hazards model with ramipril interaction term
FDA analyses by J Lawrence, in FDA statistical review authored by J Mele, NDA 21071, DFS 3 Jul 07. Conditional MLE of odds ratio, Fisher exact test p-value
4 From published RECORD interim analysis (Home 2007). MI = acute myocardial infarction. Cox proportional hazards regression stratified by background medication.
5 From PROactive study report, NDA 21073 suppl 026, Tables 11.1 (pg 87), 11.g (pg 80), 11.h (pg 81). Cox proportional hazards model with treatment as only covariate. MI in composite = nonfatal MI excluding silent MI; separate analysis of component of nonfatal MI excluding silent MI was not provided. For all nonfatal MI (including silent MI), HR = 0.83 (0.65, 1.06), p=0.1312. Stroke events in composite not specified as SAE.

There are several limitations to viewing this endpoint across data sources; some of these include:

- Between data sources, the patient populations are heterogeneous in terms of cardiovascular risk factors, duration of diabetes, and other important characteristics.
- Within the pooled studies, heterogeneity exists, and therefore pooling for an overall estimate may not be appropriate. Please refer to Ms. Mele's statistical bricfing paeket for estimates for the individual meta-groups, which she carcfully selected as more appropriate pools for comparisons.
- Methods of ascertainment differed between data sources. There are likely differences in the precise sets of cardiovascular adverse event terms that were ineluded within each of the components. For the poolcd studies, events were migrated from WHO terms to MedDRA terms.
- Not all events were adjudicated. In ADOPT, none were adjudicated. In DREAM and PROactive, essentially all were. Results in RECORD are presented by adjudieation status. In the pooled studies database, CV death and MI were adjudicated, but stroke was not. Definitions used for adjudication varied across studies.
- Event rates in somc data sources were low, increasing uncertainty; a few added events to one treatment group or another could change an estimate considerably.
- Duration of study varied; in the pooled studies 38/42 studies were ≤ 6 months in duration. The large prospective trials are much longer.
- Analysis models differed somewhat.

These limitations are not unique to this particular endpoint, however; virtually any endpoint one chose would have similar coneerns regarding interpretability of cardiovascular event data across data sources. It is important to bear in mind that the meta-analysis itself, which has raised this concern of cardiovascular risk, is a retrospective identification of selected endpoints across different clinieal trials with no pre-defined criteria for eoding of CV events.

Because of these limitations (and possibly other weaknesses), firm conclusions from the above table are not possible. Some observations inelude:

- For the eomposite of CV death, stroke and MI, for the two sourees of cardiovascular outeome data (RECORD for RSG and PROactive for PIO), hazard ratios are <1, and confidence intervals overlap. For the other trial data sourees, hazard ratios were generally slightly >1; statistical signifieanee was not noted for any one analysis. There appeared to be an interaction between RSG and ramipril in the DREAM study.
- For cardiovascular mortality, there was variability in the estimates, depending on the data source, and on the treatment comparison. The differences between treatment groups were not statistically significant. For the two cardiovascular outcome study data sources, hazard ratios are <1, and confidence intervals overlap. For myocardial infarction, hazard ratios were generally >1, and confidenee intervals generally included unity. In DREAM, there again appeared to be an interaetion between RSG and ramipril. For the comparison of RSG to PBO in DREAM, the OR was <1, but when considering RSG + ramipril eompared to ramipril alone, the OR was higher, and there was a significant difference between treatment groups. The PROactive study report presented the composite, but it appears that the study report did not present an analysis for the myoeardial infarction component defined for the eomposite.
- For stroke, estimates varied across data sources, with multiple HRs <1, and multiple HRs >1.

A noteworthy observation is that the incidence of all-cause mortality (which requires no adjudication) is similar between rosiglitazone and eomparators in all long-term controlled trials for which such data are available.

Table M2: Incidence of All-Cause Mortality in Long-term Controlled Trials		
Clinical Trial	**Rosiglitazone**	**Control**
ADOPT	2.3%	2.2% (SU) and 2.1% (MET)
DREAM	1.1%	1.3% (placebo)
RECORD (based on interim analysis)	3.3%	3.6% (MET/SU combination)

SUMMARY

An increased risk of cardiac ischemia was identified in a pooled analysis of 42 controlled clinical studies of rosiglitazone in patients with T2DM. The majority of the studies were of short duration with average treatment exposure of approximately 180 days (6 mos) and no systematic or rigorous follow-up of patients for CV events. Of the 14,237 patients, only 1243 (8.7%) were studied for at least one year; 716 (5%) received rosiglitazone alone or in combination with some other anti-diabetic therapy for at least one year. The studies considered in this pooled analysis also involved diverse treatment regimens including monotherapy, combination therapy, placebo vs aetive comparator, add-on vs initial therapy, etc. Different diabetic treatment regimens utilized often reflect patient populations with different baseline risk factors for cardiovascular events. Perhaps reflecting this heterogeneity in the pooled clinical trial database, are the following observations made in Ms. Mele's review:

- rosiglitazone was associated with a greater risk of ischemia in previously-treated patients than in treatment-naïve patients
- the risk of cardiac ischemia was increased in placebo-controlled studies with an OR of 1.6 (p=0.02) whereas active-controlled studies had an OR of 0.8 (p=0.8)
- combined use of rosiglitazone and metformin is associated with a higher risk of ischemia than metformin alone; however, these findings are not consistent across the 10 studies contributing to this subgroup and there was marked heterogeneity aeross these studies
- a consistent increase in risk of cardiac ischemia was observed in all studies in which rosiglitazone was added on to insulin; exclusion of these five studies from the meta-analysis resulted in no significant inerease in ischemic risk
- evaluation of time-to-event for studies from the meta-analysis that are > 1 yr in duration shows no differenee in risk in the composite endpoint of stroke/MI/CV death and serious ischemic events.

Since the eurrent opinion of increased cardiac ischemie risk associated with rosiglitazone is not based on findings from a single trial but from a pooling of multiple, heterogeneous trials, one might also want to compare the findings from the meta-analysis with the results of the long-term controlled studies. Indeed, many of the observations made on the meta-analysis may be better addressed with these long-term controlled studies. In particular, risk in treatment-naïve patients can be addressed by DREAM and ADOPT, which specifically studied such patients. Results from ADOPT and RECORD may clarify the observation in the meta-analysis of lower risk in active control trials, as these two studies compared rosiglitazone to other anti-diabetic agents. RECORD and perhaps BARI-2D may provide information on the risk of combining rosiglitazone and metformin. As these two studies enrolled a patient population with greater baseline risk for CVD, the use of nitrates and ACE-inhibitors may be in a sufficient number of patients to further evaluate any interaetion with rosiglitazone and the risk of eardiac ischemia. Finally, the observation that longer term studies in the meta-analysis had similar risks between rosiglitazone and comparators highlights the importance of looking to these long-term controlled studies to confirm this finding.

The risk of ischemia associated with rosiglitazone and insulin co-administration is not likely to be addressed with these long-term studies. This observation will need further discussion by the committee members as the following questions are considered at the close of GSK and FDA presentations.

QUESTIONS TO COMMITTEE MEMBERS

1. Please comment on the strengths/limitations of the meta-analysis of the 42 controlled clinical studies submitted by GSK to the Agency on defining cardiac ischemic risk for Avandia. Comment on the following areas is of particular relevance:
   - types of studies selected (e.g., comparison groups)
   - patient populations
   - treatment duration of studies
   - endpoints (total ischemic events, composite of stroke/MI/CV death) and their ascertainment

2. Please comment on the completed and on-going long-term clinical studies for Avandia with respect to whether cardiac ischemic risk identified in the meta-analysis can be addressed by:
   - DREAM
   - ADOPT
   - RECORD
   - BARI-2D

3. Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus (VOTE requested)?
   - If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes mellitus?

4. Does the overall risk-benefit profile of Avandia support its continued marketing in the US (VOTE requested)?
   - If yes, please comment on what FDA should do to maximize the risk-benefit considerations (e.g., limit to certain patients, incorporate a boxed warning....)

REFERENCES

Brooks M et al 2006. Hypotheses, design and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Am J Cardiol 97(suppl):9G-19G

Colhoun H et al 2004. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364(9435):685-96

Diabetes Control and Complications Trial Research Group 1998. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 116(7):874-86

Diabetes Control and Complications Trial Research Group 1993. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. NEJM 329:977-86

Dormandy J et al 2005. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. Lancet 366:1279-89

DREAM Trial Investigators 2006. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 368:1096-105

DREAM Trial Investigators 2004. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. Diabetologia 47:1519-27

Holman R et al 2006. Letter to editor regarding published PROactive study results. Lancet 367:25

Home P et al 2005. Rosiglitazone evaluated for cardiac outcomes and regulation of glycaemia in diabetes (RECORD): study design and protocol. Diabetologia 48:1726-1735.

Home P et al 2007. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. NEJM 357: 1-11, online publication 5 Jun 07

Lubson J and Poole-Wilson P 2006. The DREAM Trial (letter to editor). Lancet 368:2050

Kahn SE et al 2006. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy (ADOPT). NEJM 355:2427-2443.

EXHIBIT 17

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

From: Robert J. Meyer, MD
Director, Office of Drug Evaluation II

Gerald J. DalPan, MD, MHS
Director, Office of Surveillance and Epidemiology

Date: Monday, July 09, 2007

Topic: Introduction of issues for the Advisory Committee meeting on July 30th, 2007 to discuss cardiovascular ischemic events with Avandia (Rosiglitazone)

BACKGROUND

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is characterized by hyperglycemia and is often accompanied by other conditions, such as dyslipidemia, obesity, and hypertension. The prevalence of T2DM has increased to epidemic proportions in the United States in the past several decades, in part due to the rising rate of obesity in the adult and pediatric population. The chronic complications of diabetes, such as kidney disease, blindness, peripheral vascular disease, and cardio/cerebrovascular disease, further contribute to the public health crisis that is and will result from the rising prevalence of this important disease.

The pathogenic mechanism for T2DM is multifactorial, with impaired glucose tolerance and insulin resistance being an early hallmark of pre-diabetes. The disease process progresses with beta-cell function declining, until the reduced capacity for insulin secretion becomes inadequate to maintain normoglycemia. Derangements in hepatic glucose metabolism are also present, and more recently it has been recognized that gastrointestinal peptides, such as incretin hormones and amylin, play key roles in the regulation of serum glucose levels, particularly in the post-prandial state. The secretion of the incretins also becomes deranged as T2DM progresses.

The differing pathogenic factors in the progression of T2DM have led to the development of therapeutics with different mechanisms of action, each targeted at one or more of the multiple defects contributing to dysglycemia. While preventive measures and lifestyle intervention (e.g., proper diet and exercise) should remain the cornerstone of management, T2DM is a progressive disease with worsening glycemia over time that

makes initiation of drug treatment *and* the use of a combination of different drugs subsequently the rule, more than the exception, as few patients can ultimately be controlled over the long term with diet and exercise alone.

The following table summarizes the currently available agents for the treatment of T2DM.

Table 1. Available Agents for the Treatment of Type 2 Diabetes Mellitus

Drug Class	Route of Administration	Expected HbA1c Reduction (Monotherapy)	Side Effects
Insulin	Subcutaneous injection (inhaled, short-acting insulin recently approved)	> 1.5 to 2.5% (no dose limit)	Hypoglycemia, weight gain
Sulfonylureas (SUs)	Oral	1.5%	Hypoglycemia, weight gain, probable cardiac ischemic risk with certain SUs
Biguanide/Metformin	Oral	1.5%	Rare lactic acidosis, contraindicated in patients with renal impairment
Alpha-glucosidase inhibitors	Oral	0.5 to 0.8%	GI side effects
TZDs/PPAR agonists	Oral	0.5 to 1.5%	Anemia, weight gain, edema, heart failure, cardiac ischemic risk; potential cancer risk (bladder cancer signal with pioglitazone
Glinides	Oral	1 to 1.5%	Hypoglycemia
Amylin analogues	Subcutaneous injection	0.5 to 1.0%	GI side effects
GLP-1 analogues*	Subcutaneous injection	0.4 to 0.8%	GI side effects
DPPIV-inhibitors**	Oral	0.5 to 0.9%	Limited clinical experience; nonclinical safety signals for many in development

*Exenatide is the only approved GLP-1 analogue and is not indicated for use as monotherapy. Efficacy data are for add-on therapy to metformin or SU in T2DM;
**Sitagliptin is the only approved DPP4-inhibitor (approved 10/06).

FDA approves agents for T2DM on the basis of the drug leading to better glycemic control, as manifested by hemoglobin A1c (HgbA1c) determinations, a measure which integrates glycemia over time. Improved glycemic control is of itself a desirable outcome in DM, as elevated blood sugars lead to troublesome symptoms and signs, such as fatigue, polyuria, and polydypsia, and can have more serious immediate consequences, such as an elevated risk of infections and, in extreme instances, hyperosmolar coma. In this sense, utilizing HgbA1c as the endpoint for the approval of drugs to treat T2DM does not represent a surrogate. Improved glycemia over 6 months (the duration of a typical DM trial) is a direct benefit to the patients. Indeed, the labeling claims for oral hypoglycemic agents are specific to improvement in glycemia (e.g., "AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus"), with no wording suggesting a modification in long-term DM sequelae. Nonetheless, long-term improvements in HgbA1c would be expected to decrease the risk of microvascular complications (renal, ophthalmologic, neurologic) and, it is hoped, the macrovascular complications (stroke, MIs, peripheral arterial disease) that are the sequelae of long-standing DM. So, while improved "short-term" glycemic control is a direct benefit to the patient, it would be a significant concern if an agent approved for treating T2DM were to increase the risk of cardiac ischemic events, particularly if there were good evidence that other agents approved to treat T2DM did not do so, especially other agents in the same class.

While new drugs for T2DM have comparatively robust databases at the time of approval, the accumulating clinical experience with each drug and each class of drugs post-arpproval, either as monotherapy or as part of a multiple-drug regimen, has brought to light new safety concerns. This is certainly true with the thiazolidinediones(TZDs), the class that includes rosiglitazone. TZDs are selective ligands of the nuclear transcription factor peroxisome-proliferator-activator-receptor-γ (PPAR-γ). Also referred to as PPAR-γ agonists, these drugs have been developed to target the insulin resistance associated with T2DM. Troglitazone (Rezulin®) was the first TZD approved (in 1997). However, shortly after its approval and marketing, severe cases of hepatotoxicity were observed, with cases necessitating liver transplant and/or resulting in death being reported to FDA post-marketing. In 1999, the FDA approved rosiglitazone (Avandia®) and pioglitazone (Actos®). Clinical trial experience and close post-marketing surveillance of these two compounds have shown much more favorable risk profiles for hepatotoxicity with these agents, compared to troglitazone , which was withdrawn from the market in March 2000. As a class, PPAR agonists are associated with anemia, hemodilution, weight gain, edema, and exacerbation or development of heart failure. The pathogenesis of edema with PPARs appears to be complex, but likely relates to a direct pharmacological action, as it has clearly proven to be a class effect. Indeed, both rosiglitazone and pioglitazone are similarly associated with anemia, weight gain, edema, and risk of heart failure. The risk for significant edema precipitating or exacerbating heart failure was known at the time of approval, but has also led to numerous labeling revisions for both of these drugs as marketing experience and the results of further trials have been reviewed by the agency. This issue will shortly be the subject of a boxed warning for both agents. While this is an important class effect, it is not the subject of the Advisory Committee meeting itself.

While the risk for edema and heart failure has been well-appreciated and described for TZDs, the effect of these drugs on cardiovascular ischemic risk had been less of a known concern. There were early concerns raised by some with regard to the potential for rosiglitazone to have a less favorable effect on long-term macrovascular disease outcomes due to some disadvantageous changes in lipid profiles resulting from rosiglitazone therapy compared to pioglitazone (which has more PPAR-alpha activity, similar to the fibrate class of drugs). In December 2003, the World Health Organization published an analysis of adverse reaction reports from the WHO Database that included a general discussion of thiazolidinediones (TZDs) and a datamining signal for "cardiac disease" overall, which would include both heart failure and ischemic terms. This finding resulted in GSK examining data from the randomized controlled trials (RCTs) with rosiglitazone to further investigate CV risks in general with Avandia. In October 2005, GSK submitted to FDA summary slides showing preliminary results from a pooling of results from RCTs that further raised the concern that rosiglitazone may be associated with ischemic cardiac events. GSK proposed a formal analysis plan to provide a more definitive, formal examination of the pooled data RCTs.

Preceding the receipt of the formal GSK meta-analysis of the phase 2 and 3 RCTs with rosiglitazone, FDA completed a review of a 52-week study performed in patients with pre-existing heart failure. This study was done to examine if rosiglitazone led to decrements in cardiac function as assessed by echocardiography, as an exploration of the mechanism of CHF. In this study, a blinded adjudication committee looked at cardiac events, focusing on CHF events and overall CV deaths and hospitalization. While angina and MIs were not separately adjudicated, they were captured from case report forms. While there were no differences between rosiglitazone and placebo in echocardiographic assessments, there was a numerical disadvantage in cardiac events, both in terms of CHF and ischemic events. FDA considered these findings to be of sufficient importance to place the results of this study with the first WARNING about cardiac adverse effects in the labeling in April of 2006. This was the first specific mention in labeling of a potential association of rosiglitazone with cardiac ischemia, whose risk was in the warning in tabular form.

FDA received the submission detailing the GSK-conducted integrated statistical analysis of 42 phase 2 and 3 randomized controlled clinical trials (RCTs) of rosiglitazone in patients with T2DM in August of 2006 (including the echocardiographic study detailed above). These data were contained in a labeling supplement that also contained the findings from an observational cohort study commissioned by GSK and conducted by i3 Research, a contract research organization. Both these databases focused on characterizing the risk of heart failure as well as the cardiac ischemic events associated with rosiglitazone use. GSK's summary of their meta-analysis showed an apparent imbalance of cardiovascular ischemic events with a hazard ratio of approximately 1.31 (that is, a 31% increase in cardiac ischemic events with rosiglitazone compared to the comparator group). On the other hand, the observational cohort study (Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents) showed no such increased risk of cardiac ischemic risk. On their face, these two studies provided conflicting data on this very important issue. For this reason and because of some significant concerns on

the part of the FDA biometrics staff with the details of how GSK conducted its meta-analysis, FDA believed it was important to conduct its own thorough and complex analysis of these same RCT data, which has only recently been completed. FDA also thoughtfully assessed the results of the observational cohort study. You will see and hear more details on FDA's findings for both studies in this briefing document as well as at the Advisory Committee meeting itself.

Other data relevant to the question of the potential for rosiglitazone to cause cardiac ischemic events became available subsequent to GSK's submission of their RCT meta-analysis in August of 2006. In September 2006, the results from a study of rosiglitazone versus placebo (with a 2x2 factorial design also examining ramipril vs. placebo) used in prediabetic patients to delay the onset of diabetes was published. [1] This study, named DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), was an independent study (i.e., not conducted by GSK) coordinated by McMaster University. This study will be discussed at the meeting itself and the report as published is contained in this background package.

In December 2006, the results of ADOPT (A Diabetes Outcome Progression Trial) were published. [2] ADOPT was conducted by GSK as a phase 4 commitment made at the time of approval of rosiglitazone. It was a large, long-term diabetes trial comparing the time to failure of monotherapy with rosiglitazone, metformin, or glyburide, as well as assessing relative safety, including CHF. In ADOPT, rosiglitazone performed the best on the primary efficacy outcome of interest (length of time successfully treated with monotherapy), with glyburide having both the highest rate of treatment failure and the highest rates of discontinuation and missing data. For CV ischemic outcomes, rosiglitazone compared favorably to metformin, with both appearing somewhat less favorable than glyburide. Although the results of this study were published in December 2006, the primary data were submitted to FDA by GSK in February 2007 and we do not have a final FDA analysis to present at this time. Ongoing review of cardiovascular events will be presented and are discussed elsewhere in this briefing document.

These various datasets present an array of somewhat inconsistent findings that complicate the interpretation of the available data regarding the effect of rosiglitazone on cardiac ischemic events. Nonetheless, given the findings from the RCT meta-analysis, FDA views this signal with considerable concern.

Following a high level discussion of the issue of the cardiac safety of the PPAR agents (rosiglitazone and pioglitazone) at a Center-wide briefing in April 2007, the following was decided:

1. Because of persistent reports in the spontaneous adverse events reporting system of the PPAR agents being utilized in a manner inconsistent with labeling and what is known about risk of heart failure, the prominent warnings with regard to the risk for heart failure and edema with these agents would be appropriate for a

1 Lancet September 23, 2006; 368: 1096 - 1105
2 NEJM 355;23 December 7, 2006

boxed warning for both rosiglitazone and pioglitazone. (This action is ongoing and is not the subject of this Advisory Committee meeting).

2. With regard to the signal of CV ischemic events with rosiglitazone, FDA was to call in the sponsor (GSK) for a meeting in the near future to discuss their thinking on this risk and to see if they could provide other data or information that would better clarify or quantify the signal of risk. (That meeting took place on May 16th, 2007). In the meantime, FDA was to work on a communication strategy for alerting the public to our ongoing concerns and plans, above and beyond the data already in the rosiglitazone labeling on CV ischemic events.
3. FDA planned to take both the issue of heart failure for both drugs and the CV ischemic signal to an Advisory Committee meeting in the late summer or early fall.

With the publication by Dr. Nissen and Ms. Wolski of their meta-analysis of the risk cardiac ischemic events with rosiglitazone and the accompanying editorials by Drs. Psaty and Furberg,[3] FDA accelerated it public message about its ongoing work with regard to the CV ischemic signal and also moved forward the date for the Advisory Committee meeting, narrowing the focus of the meeting to the CV ischemic issue with rosiglitazone. We should note that while Dr. Nissen's meta-analysis and the editorials engendered considerable public notice and concern, the specific conduct and results of this meta-analysis, performed out of necessity on study level data, will not be a focus of this Advisory Committee meeting nor of this background document. This is because we believe the results of the analysis performed by GSK and subsequently by the FDA on the more granular individual datasets do not greatly differ from that of Dr. Nissen and Ms. Wolski in a qualitative sense. Importantly, though, we believe that the FDA analysis of the data, including patient level data, is more robust than would be possible for an analysis utilizing study-level data alone.

Finally, due to concerns over the findings in the meta-analysis, GSK had the data monitoring committee for its ongoing RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial perform an interim analysis of cardiovascular safety. This interim analysis was recently published, and a copy of the publication is included in the background package.. RECORD is an ongoing, large, randomized, controlled trial of rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to metformin and a sulfonylurea in patients not adequately controlled on their prior single-agent therapy with either metformin or a sulfonylurea. While the study is necessarily open label (this being a long-term treatment trial where adjustment of therapy is required), the adjudication of the cardiac events is blinded to treatment assignment. The design of the RECORD study and the results of the interim analysis will be presented at the Advisory Committee meeting and the reports of the interim analysis as published are contained in the background document.

3 NEJM online 10.1056/NEJMoa072761; NEJM online 10.1056/NEJMe078099

Conclusions: Since the prevalence of T2DM is of epidemic proportions in the US, and because the use of rosiglitazone is widespread, it is of high public health importance to characterize and quantify the risk of ischemic CV events with rosiglitazone .. It is also important to place any risk into context of what is known about the risks of other available therapies for T2DM, including the other PPAR agent – pioglitazone. For instance, based on a decades old study with tolbutamide, the sulfonylurea agents all carry a warning about the potential for inducing myocardial ischemia with this class of drugs. Since non-pharmacologic treatment of T2DM is not an option as the disease progresses, one needs to place the data with rosiglitazone into context with what is known and/or not known with alternative therapies, including pioglitazone. In addition, it is necessary to place any risk into context with what is known about the benefits of the drug.

In this document and in the sponsor's and FDA's presentations at the Advisory Committee meeting, along with the public comments, we hope to provide the committee with as complete a set of data as possible to inform the committee's discussion and subsequent recommendations. We look forward to the committee advising FDA on the interpretation of these data, and on any conclusions or actions that should be taken based on them.

We look forward to a thorough and reasoned discussion of this complex, important matter and thank you in advance for the vital public health contribution you are making through your participation in this important meeting.